Is overreliance on short-acting β_2-agonists associated with health risks in the older asthma population?

Teresa To[1,2,3], Jingqin Zhu[2,3], Emilie Terebessy[2], Kimball Zhang[2,3], Andrea S. Gershon [1,2,3,4,5] and Christopher Licskai[6,7]

[1]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada. [2]The Hospital for Sick Children, Toronto, ON, Canada. [3]ICES, Toronto, ON, Canada. [4]Division of Respirology, Dept of Medicine, University of Toronto, Toronto, ON, Canada. [5]Sunnybrook Health Sciences Centre, Toronto, ON, Canada. [6]Schulich School of Medicine and Dentistry, Western University, London, ON, Canada. [7]London Health Sciences, Victoria Hospital, London, ON, Canada.

Corresponding author: Teresa To (teresa.to@sickkids.ca)

Shareable abstract (@ERSpublications)
These results in older people with asthma add strength to previously documented associations of SABA use, severe asthma exacerbations and death. Clinicians may consider these safety results when prescribing and assessing new therapeutic recommendations. https://bit.ly/34Gr56P

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Abstract

Recent Global Initiative for Asthma (GINA) recommendations reduce the role of short-acting β_2-agonist (SABA) premised on the associated exacerbation risk. The widely accepted SABA risk profile is based on limited data described 30 years ago. This GINA paradigm shift demands an examination of SABA risks in a modern therapeutic era. Recent studies confirm that SABA overuse is common and associated with adverse outcomes. This study aimed to determine associations between SABA use, all-cause mortality and asthma exacerbations in an older North American asthma population.

In this population-based cohort study, individuals with prevalent asthma (2006–2015) aged ⩾65 years, eligible for provincial drug coverage, were included. Annual SABA canisters filled (0, 1–2, 3–5, ⩾6) was the primary exposure. Hazard ratios (HRs) with 95% CIs were estimated using Cox proportional hazard regression, adjusted for confounders.

There were 59 533 asthma individuals; 14% overused SABA (⩾3 canisters annually). Compared to those who used <3 canisters, the adjusted HRs of death for those who used 3–5 and ⩾6 canisters were 1.11 (95% CI: 1.02–1.22, p=0.0157) and 1.56 (95% CI: 1.41–1.71, p<0.0001), respectively. Severe asthma exacerbation rates for ⩾3 and <3 canisters/year were 7.5% and 2.1%, respectively. The adjusted HRs of severe asthma exacerbations were 1.59 (95% CI: 1.40–1.82, p<0.0001) and 2.26 (95% CI: 1.96–2.60, p<0.0001) in those who used 3–5 and ⩾6 SABA canisters per year, respectively.

In Canada, 1 in 7 individuals with asthma overused SABA associated with increased risks of severe asthma exacerbations and death. The adverse impacts of SABA overuse continue 30 years after early publications.

Introduction

Short-acting β_2-agonist (SABA) bronchodilators have figured prominently in asthma care for over 50 years, dating to a time when asthma was considered a disease of bronchoconstriction. The introduction of inhaled corticosteroid (ICS) combined with formoterol as maintenance and reliever therapy signalled a shift towards the use of ICS whenever bronchodilators were required. Maintenance and reliever therapy serves to reduce severe exacerbations compared to a SABA *p.r.n.* strategy [1]. In their 2019 update, the Global Initiative for Asthma (GINA) triggered a seismic shift in the asthma treatment paradigm [2]. By 2021, ICS-formoterol had supplanted SABA as the preferred reliever approach for all patients with asthma (Track 1). SABA is now an alternate choice where Track 1 is not possible or if a "patient with no exacerbations on their current therapy" prefers SABA *p.r.n.* (Track 2) [3].

GINA cites two reasons for changing the treatment paradigm, the new body of evidence in mild asthma demonstrating that ICS-formoterol as reliever reduced exacerbations compared to SABA and SABA-related safety concerns [3]. Concerns about the mortality risk of SABA therapy were ignited by an epidemic of asthma deaths in New Zealand in the 1980s [4]. SPITZER and colleagues [5] added observational data in 1992 defining an association between SABA use, near-fatal asthma and death, and further defined a dose response. 30 years later, concerns about SABA safety remain.

Recent studies suggested SABA reliance or overuse (⩾3 SABA canisters annually) poses a problem in Europe and other developed countries. The global study by SABINA (SABA use IN Asthma) suggested that as many as one-third of asthma patients overused SABA [6, 7]. For example, a Swedish cohort study linking data with 365 324 asthma patients found that SABA overuse was associated with significantly increased risks of exacerbation and mortality [7]. In Italy, the 2-year follow-up study using the Longitudinal Patient Database of over 22 000 patients found that SABA overuse was common among SABA users with an average of four SABA canisters purchased annually [8]. Moreover, the use of >2 SABA canisters annually was associated with a 30% higher likelihood of experiencing exacerbations [8]. Similarly, in the UK, amongst the 336 412 patients with linked hospital data, high SABA inhaler use was significantly associated with an increased risk of exacerbations, asthma-related hospitalisation and outpatient health services use (HSU) [9].

There is a small but growing number of modern population-based studies quantifying the association between SABA overreliance and adverse outcomes. Observational data are strengthened when multiple studies across different populations identify the same effect and magnitude. Currently, where there is a choice of reliever therapy, it is important to define the relative safety of existing therapies, particularly when adverse outcomes include hospitalisation and death. Thus, further population-based research is needed to determine if there is an increased risk of adverse outcomes associated with SABA overuse to provide clarity about the safety of these widely used medications. The objective of this study was to determine the associations between SABA use, all-cause mortality and severe asthma exacerbations (SAEx) in an older Canadian asthma population.

Methods

Study design and population

The association between SABA use and adverse health outcomes was investigated using a cohort design.

Inclusion criteria

The cohort included Ontario residents aged 65–99 years with prevalent asthma in the decade between 1 April 2006 and 31 March 2015. Asthma diagnosis was determined based on an administrative case definition of ⩾1 hospitalisation for asthma or ⩾2 outpatient visits for asthma in 2 consecutive years. This definition has been clinically validated by chart abstraction with a sensitivity of 84% and a specificity of 77% [10]. The study population included individuals who met this definition of asthma diagnosis. The index date was defined in the following order: the first date of prescription of asthma medication (see drug list in supplementary table E1) between 1 April 2006 and 31 March 2015 through a publicly funded provincial drug plan, asthma HSU if there was no asthma medication, or asthma-related HSU if there was no asthma medication or asthma HSU. Public drug coverage is available through the Ontario Drug Benefit (ODB) programme for those aged 65 years and older, and those registered in social assistance programmes, along with their dependents.

Exclusion criteria

The study cohort was linked to the Ontario population-based COPD database to exclude individuals who may have a co-diagnosis of asthma and COPD or “flip-flop” diagnosis of asthma and COPD. The COPD case definition has been validated and demonstrated a sensitivity of 85.0% and a specificity of 78.4% [11]. Individuals excluded from the cohort included those who were ever diagnosed with COPD, congestive heart failure, cystic fibrosis, lung cancers, Crohn’s disease, ulcerative colitis, rheumatoid arthritis or bronchiectasis, and those who did not have data on age, an Ontario residence code or a valid health card number.

Data sources

This study used routinely collected health administrative data for Ontario where there is a publicly funded single-payer healthcare system. Health administrative data were linked using unique encoded identifiers at ICES, formerly known as the Institute for Clinical Evaluative Sciences. Data on emergency department (ED) visits were captured through the National Ambulatory Care Reporting System and coded using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada

(ICD-10-CA). Data on prescriptions filled were captured through ODB, and specific drugs were identified using their unique Drug Identification Number. Patients' age, sex, residence postal code, income and date of death were captured through the Provincial Registered Persons Database. Date of asthma diagnosis was captured through the Ontario Asthma Surveillance Information System (OASIS; https://lab.research.sickkids.ca/oasis/).

Exposure and outcome definitions

The primary exposure was the number of SABA canisters filled (see complete list in supplementary table E1 including drug names). Baseline exposure to SABA was categorised based on SABA usage during the 1 year post the index date. The follow-up period is from the subjects' first day after the baseline period to their death, moving out of Ontario, or the end of the study period on 31 March 2021, whichever occurs first. The cohort was followed from exposure for a maximum of 5 years or till 31 March 2021 to ascertain outcomes. The primary outcome was all-cause mortality and severe asthma exacerbation (SAEx). A SAEx was defined as an ED visit or a hospital admission for asthma and identified using ICD-10-CA codes (J45 and J46).

Covariates

Regression models were adjusted for potential confounders including age, sex, number of comorbidities, prevalence of asthma exacerbation at baseline, Ontario Marginalization Index (ON-Marg, deprivation and dependency), rurality and asthma medication use at baseline. Socioeconomic status (SES) was measured by proxy, using the ON-Marg [12]. ON-Marg provided a measure of marginalisation at the population-level based on Census information using four dimensions: material deprivation, residential instability, dependency and ethnic concentration. Based on each participant's residence postal code, they were assigned a score from 1 (least marginalised) to 5 (most marginalised) for each dimension. Residence was rural if the individual resided in a community with $\leqslant$10 000 people, or urban if otherwise true. Baseline use of asthma medication was from usage during the 1 year post the index date. Asthma medications were grouped into combinations of ICS, ICS combined with long-acting β_2-agonist (LABA), SABA, short-acting muscarinic (SAMA) or long-acting muscarinic (LAMA). SAEx during baseline and asthma medications during baseline were included in the analysis as a proxy measure to adjust for baseline asthma severity. Number of comorbidities (diabetes, hypertension, angina, stroke, ischaemic heart disease, acute myocardial infarction; see ICD-10-CA codes in supplementary table E2) were also included as confounding factors in the regression analysis.

Statistical analysis

Statistical differences in baseline characteristics by number of SABA canisters per year were examined using the Chi-squared statistics for categorial variables and ANOVA for numeric variables. Cox proportional hazard regression was used in univariable and multivariable analyses to account for the time from baseline SABA exposure to outcomes. The unadjusted and adjusted hazard ratios (HRs) for all-cause mortality, SAEx and levels of SABA use served as the primary measures of effect. For variables that did not meet the proportional hazard assumption of the Cox regression, a "stratified Cox model" was used [13]. Forest plots were also used to compare adjusted HRs with 95% CIs across subgroups. All statistical analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA), and forest plots were generated using the *forestplot* package in R statistical computing software version 3.3.3 (https://www.r-project.org/). Ethics approval exemption was obtained from the Hospital for Sick Children Research Ethics Board (Toronto, Ontario, Canada).

Results

Population characteristics

There were 59 533 individuals aged 65–99 years with prevalent asthma between 1 April 2006 and 31 March 2015. Of these, 8465 (14.2%) filled $\geqslant$3 SABA canisters at baseline. During the 5-year follow-up, a total of 7684 (12.9%) died of all-causes and 1726 (2.9%) had SAEx (table 1). The cohort consisted of 67.3% females, largely (59.9%) from areas of middle to high income quintiles, and the majority (90.5%) resided in urban areas.

The distributions of covariates across the four groups of SABA users (0, 1–2, 3–5, $\geqslant$6 canisters per year) were similar though statistically different due to large population sizes. Of note is the difference in baseline asthma medication use. Asthma individuals who used a higher number of SABA canisters also had a higher percentage use of other asthma medications including ICS or ICS-LABA.

TABLE 1 Characteristics of the study population and baseline medication use by number of short-acting β_2-agonist (SABA) canisters (n=59 533)

Covariates	Number of SABA canisters				Total	p-value[#]
	0	1–2	3–5	⩾6		
Subjects n	33 332	17 736	5332	3133	59 533	
Participant factors						
Sex n (%)						
Female	21 898 (65.7)	12 561 (70.8)	3645 (68.4)	1982 (63.3)	40 086 (67.3)	<0.001
Male	11 434 (34.3)	5175 (29.2)	1687 (31.6)	1151 (36.7)	19 447 (32.7)	
Age at index date years						
Mean±SD	69.80±6.12	69.55±5.82	69.38±6.08	69.35±6.26	69.67±6.04	<0.001
Median (IQR)	67.00 (65.00–73.00)	67.00 (65.00–72.00)	66.00 (65.00–72.00)	66.00 (65.00–72.00)	67.00 (65.00–72.00)	<0.001
Age group at index date years, n (%)						
65–69	21 254 (63.8)	11 551 (65.1)	3536 (66.3)	2080 (66.4)	38 421 (64.5)	<0.001
70–74	5533 (16.6)	3044 (17.2)	841 (15.8)	476 (15.2)	9894 (16.6)	
75–79	3415 (10.2)	1727 (9.7)	498 (9.3)	300 (9.6)	5940 (10.0)	
80–89	3130 (9.4)	1414 (8.0)	457 (8.6)	277 (8.8)	5278 (8.9)	
Age at asthma prevalence years						
Mean±SD	59.73±9.74	59.40±9.59	59.98±10.47	59.62±10.85	59.64±9.83	<0.001
Median (IQR)	59.00 (52.00–66.00)	59.00 (52.00–66.00)	60.00 (51.00–67.00)	59.00 (50.00–67.00)	59.00 (52.00–66.00)	0.004
Years of asthma at index date						
Mean±SD	10.03±6.61	10.12±6.85	9.32±7.07	9.60±7.09	9.97±6.76	<0.001
Median (IQR)	10.63 (4.14–15.16)	10.68 (3.65–15.53)	9.78 (1.72–14.99)	10.19 (2.25–14.95)	10.57 (3.68–15.23)	<0.001
Baseline asthma medication use, n (%)						
No asthma medication	20 672 (62.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 672 (34.7)	<0.001
ICS only or ICS-LABA	11 653 (35.0)	3988 (22.5)	1742 (32.7)	1134 (36.2)	18 517 (31.1)	
SABA only	0 (0.0)	6292 (35.5)	1100 (20.6)	491 (15.7)	7883 (13.2)	
Other asthma medication	1007 (3.0)	7456 (42.0)	2490 (46.7)	1508 (48.1)	12 461 (20.9)	
Socio-demographic factors						
Neighbourhood income quintile, n (%)						
1 (lowest)	5639 (16.9)	2972 (16.8)	1051 (19.7)	704 (22.5)	10 366 (17.4)	<0.001
2	6648 (19.9)	3562 (20.1)	1133 (21.2)	726 (23.2)	12 069 (20.3)	
3	6445 (19.3)	3563 (20.1)	1073 (20.1)	642 (20.5)	11 723 (19.7)	
4	6911 (20.7)	3763 (21.2)	1048 (19.7)	522 (16.7)	12 244 (20.6)	
5 (highest)	7604 (22.8)	3843 (21.7)	1010 (18.9)	527 (16.8)	12 984 (21.8)	
Missing	85 (0.3)	33 (0.2)	17 (0.3)	12 (0.4)	147 (0.2)	
Ontario Marginalization Indices (lowest quintile is the least marginalised)						
Deprivation quintile, n (%)						
1 (least)	6953 (20.9)	3735 (21.1)	1000 (18.8)	516 (16.5)	12 204 (20.5)	<0.001
2	6752 (20.3)	3517 (19.8)	978 (18.3)	505 (16.1)	11 752 (19.7)	
3	6606 (19.8)	3506 (19.8)	989 (18.5)	616 (19.7)	11 717 (19.7)	
4	6652 (20.0)	3532 (19.9)	1190 (22.3)	710 (22.7)	12 084 (20.3)	
5 (most)	6185 (18.6)	3354 (18.9)	1135 (21.3)	766 (24.4)	11 440 (19.2)	
Missing	184 (0.6)	92 (0.5)	40 (0.8)	20 (0.6)	336 (0.6)	
Dependency quintile, n (%)						
1 (least)	5449 (16.3)	3186 (18.0)	1044 (19.6)	678 (21.6)	10 357 (17.4)	<0.001
2	5981 (17.9)	3322 (18.7)	1040 (19.5)	620 (19.8)	10 963 (18.4)	
3	6142 (18.4)	3236 (18.2)	971 (18.2)	611 (19.5)	10 960 (18.4)	
4	6528 (19.6)	3326 (18.8)	937 (17.6)	512 (16.3)	11 303 (19.0)	
5 (most)	9048 (27.1)	4574 (25.8)	1300 (24.4)	692 (22.1)	15 614 (26.2)	
Missing	184 (0.6)	92 (0.5)	40 (0.8)	20 (0.6)	336 (0.6)	

Continued

TABLE 1 Continued

Covariates	Number of SABA canisters				Total	p-value[#]
	0	1–2	3–5	⩾6		
Ethnic concentration quintile, n (%)						
1 (least)	5161 (15.5)	2846 (16.0)	830 (15.6)	461 (14.7)	9298 (15.6)	<0.001
2	5325 (16.0)	2928 (16.5)	856 (16.1)	418 (13.3)	9527 (16.0)	
3	6005 (18.0)	3135 (17.7)	848 (15.9)	455 (14.5)	10 443 (17.5)	
4	7207 (21.6)	3567 (20.1)	960 (18.0)	560 (17.9)	12 294 (20.7)	
5 (most)	9450 (28.4)	5168 (29.1)	1798 (33.7)	1219 (38.9)	17 635 (29.6)	
Missing	184 (0.6)	92 (0.5)	40 (0.8)	20 (0.6)	336 (0.6)	
Instability quintile, n (%)						
1 (least)	6470 (19.4)	3689 (20.8)	1129 (21.2)	712 (22.7)	12 000 (20.2)	<0.001
2	6539 (19.6)	3512 (19.8)	949 (17.8)	516 (16.5)	11 516 (19.3)	
3	6224 (18.7)	3264 (18.4)	975 (18.3)	560 (17.9)	11 023 (18.5)	
4	6045 (18.1)	3188 (18.0)	1017 (19.1)	535 (17.1)	10 785 (18.1)	
5 (most)	7870 (23.6)	3991 (22.5)	1222 (22.9)	790 (25.2)	13 873 (23.3)	
Missing	184 (0.6)	92 (0.5)	40 (0.8)	20 (0.6)	336 (0.6)	
Rural residence, n (%)	3046 (9.1)	1738 (9.8)	545 (10.2)	307 (9.8)	5636 (9.5)	0.015
Follow-up years						
Mean±SD	8.82±3.25	8.82±3.17	9.07±3.35	9.01±3.58	8.85±3.25	<0.001
Median (IQR)	8.50 (6.41–11.59)	8.47 (6.41–11.55)	8.75 (6.65–12.17)	8.81 (6.56–12.34)	8.53 (6.43–11.66)	<0.001
Number of comorbidities, n (%)						
0	7732 (23.2)	4029 (22.7)	1206 (22.6)	626 (20.0)	13 593 (22.8)	0.001
1	12 762 (38.3)	6940 (39.1)	2053 (38.5)	1240 (39.6)	22 995 (38.6)	
2	8260 (24.8)	4407 (24.8)	1396 (26.2)	831 (26.5)	14 894 (25.0)	
⩾3	4578 (13.7)	2360 (13.3)	677 (12.7)	436 (13.9)	8051 (13.5)	
Outcomes						
Deaths, n (%)	4487 (13.5)	1942 (10.9)	703 (13.2)	552 (17.6)	7684 (12.9)	<0.001
Severe asthma exacerbation, n (%)	446 (1.3)	642 (3.6)	343 (6.4)	295 (9.4)	1726 (2.9)	<0.001

SABA: short-acting β_2-agonist; IQR: interquartile range; ICS: inhaled corticosteroid; ICS-LABA: ICS long-acting β_2-agonist. [#]: p-values were calculated using Chi-squared statistics for categorical variables and ANOVA for numerical variables.

All-cause mortality

During the 5-year follow-up, 7684 (12.9%) individuals died of all-causes. A higher proportion of deaths was found in those who filled ⩾3 SABA canisters annually (14.8%) compared to those who filled <3 SABA canisters annually (12.6%). This corresponds to an unadjusted HR of 1.14 (95% CI: 1.05–1.25, p=0.0025) and 1.52 (95% CI: 1.38–1.67, p<0.0001) for 3–5 and ⩾6 SABA canisters annually, respectively. ICS at baseline seemed to mitigate but not eliminate the impact of high SABA utilisation. Compared to those who were taking ICS, those who were not taking any asthma medications, receiving other asthma medications or taking SABA only had significantly higher HRs for all-cause mortality. As expected, those with a higher number of comorbidities were associated with an incrementally increased all-cause mortality risk. Those who experienced SAEx in the baseline period, as a proxy of baseline asthma severity, were not statistically associated with increased risk of death.

In the multivariable Cox proportional hazard regression analyses (table 2 and figure 1), after adjusting for confounders (age, sex, number of comorbidities, prevalence of asthma exacerbation at baseline, ON-Marg (deprivation and dependency), rurality, asthma medication use at baseline), compared to SABA use of 1–2 canisters per year, we observed significantly increased all-cause mortality rates in those who used 3–5 and ⩾6 SABA canisters per year (HR=1.11 (95% CI: 1.02–1.22, p=0.0157) and HR=1.56 (95% CI: 1.41–1.71, p<0.0001), respectively).

Severe asthma exacerbations (SAEx)

We defined SAEx as an ED visit or a hospital admission for asthma. During the 5-year follow-up, there were 1726 (2.9%) SAEx amongst the study population. SAEx rates were 7.5% and 2.1% among individuals who used ⩾3 and <3 canisters, respectively. The rate of SAEx was doubled in those who used ⩾3 SABA canisters per year compared to those who used 1–2 SABA canisters per year (7.5% *versus*

TABLE 2 All-cause mortality hazard ratios (HRs) from Cox proportional hazard regressions (n=59 533)

	Unadjusted HR (95% CI)	p-value	AHR (95% CI)	p-value
Exposure				
SABA canisters per year				
0	1.23 (1.16–1.29)	<0.0001	1.07 (0.98–1.17)	0.15
1–2	1.00	(Reference)	1.00	(Reference)
3–5	1.14 (1.05–1.25)	0.00	1.11 (1.02–1.22)	0.02
⩾6	1.52 (1.38–1.67)	<0.0001	1.56 (1.41–1.71)	<0.0001
Covariate				
Deprivation quintile				
1 (least)	1.00	(Reference)	1.00	(Reference)
2	1.09 (1.01–1.17)	0.02	1.03 (0.95–1.11)	0.47
3	1.12 (1.04–1.21)	0.00	1.00 (0.93–1.08)	0.97
4	1.21 (1.13–1.3)	<0.0001	1.03 (0.96–1.11)	0.44
5 (most)	1.33 (1.23–1.42)	<0.0001	1.11 (1.04–1.19)	0.00
Dependency quintile				
1 (least)	1.00	(Reference)	1.00	(Reference)
2	1.10 (1.01–1.20)	0.02	1.03 (0.95–1.12)	0.52
3	1.15 (1.06–1.25)	0.00	1.08 (0.99–1.17)	0.07
4	1.30 (1.20–1.41)	<0.0001	1.16 (1.07–1.26)	0.00
5 (most)	1.67 (1.56–1.8)	<0.0001	1.25 (1.16–1.34)	<0.0001
Age group at index date	1.17 (1.16–1.17)	<0.0001	1.16 (1.16–1.17)	<0.0001
Male sex (reference=female)	1.09 (1.04–1.14)	0.00	1.30 (1.24–1.36)	<0.0001
Rural residence (reference=urban)	1.05 (0.97–1.13)	0.24	1.19 (1.10–1.28)	<0.0001
ICS only or ICS-LABA	1.00	(Reference)	1.00	(Reference)
No asthma medication	1.43 (1.35–1.51)	<0.0001	1.26 (1.18–1.34)	<0.0001
SABA only	1.29 (1.20–1.39)	<0.0001	1.19 (1.08–1.31)	0.00
Other asthma medication	1.26 (1.19–1.35)	<0.0001	1.16 (1.07–1.26)	0.00
Asthma exacerbation in baseline period	0.90 (0.69–1.16)	0.40	1.08 (0.83–1.39)	0.58
Number of comorbidities				
0	1.00	(Reference)	1.00	(Reference)
1	1.63 (1.51–1.76)	<0.0001	1.25 (1.15–1.34)	<0.0001
2	2.54 (2.36–2.75)	<0.0001	1.66 (1.54–1.79)	<0.0001
⩾3	3.75 (3.46–4.06)	<0.0001	2.13 (1.96–2.31)	<0.0001

AHR: adjusted hazard ratio; SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; ICS-LABA: ICS long-acting β_2-agonist.

3.6%, p<0.001). Any asthma medication use was negatively associated with risks of SAEx. Only a small percentage (3.8%) of individuals with SAEx were not taking any asthma medications, while nearly half of them were taking ICS or ICS-LABA (48.7%).

After adjusting for baseline SAEx, baseline medication use including ICS use and other confounders, compared to SABA use of 1–2 canisters per year, we observed significantly increased SAEx rates in those who used 3–5 and ⩾6 SABA canisters annually (HR=1.59 (95% CI: 1.40–1.82, p<0.0001), HR=2.26 (95% CI: 1.96–2.60, p<0.0001), respectively; table 3, figure 2).

Discussion

This Canadian population-based study of older adults with asthma showed statistically significant adverse health outcomes associated with SABA overuse. In Ontario, 1 in 7 (14%) asthma individuals overused SABA, which is associated with an 11% and 56% increased risk of death in those who used 3–5 and ⩾6 SABA canisters per year, respectively. Furthermore, there were 1.6- and 2.3-fold increased risks in SAEx among those who used 3–5 and ⩾6 SABA canisters annually, respectively. There was a risk gradient that was dependent on total exposure to SABA. Importantly, the SABA findings were durable when adjusted for baseline SAEx, a surrogate for asthma severity and control, and for baseline medication including baseline ICS use.

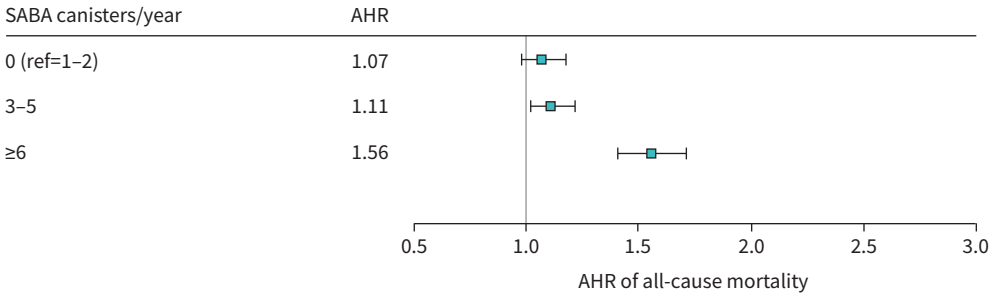

FIGURE 1 Forest plot comparing adjusted hazard ratios (AHRs) for all-cause mortality from Cox proportional hazards regression. The Cox proportional hazards regression models were adjusted for the following: age, sex, prevalence of comorbidities, prevalence of asthma exacerbation at baseline as an indicator of severity of asthma, Ontario Marginalization Index (deprivation and dependency), rurality and asthma medication use at baseline. SABA: short-acting β_2-agonist; ref: reference.

Previous literature suggests that the risk of mortality in the asthma population was multifaceted. For example, older age [14, 15], being female [15], reliance on SABA monotherapy [16, 17] as their sole treatment, and comorbid conditions (*e.g.* diabetes and hypertension) [18] were associated with a higher risk of mortality. In this study we adjusted for age, sex, controller use and comorbidities to identify SABA use as an independent risk factor. Our study results are consistent with the published findings (table 4) on SABA use and health outcomes from Sweden [7], Italy [8], Germany [19], France [20, 21], Poland [22]

TABLE 3 Severe asthma exacerbation hazard ratios (HRs) from Cox proportional hazard regressions (n=59 533)

	Unadjusted HR (95% CI)	p-value	AHR (95% CI)	p-value
Exposure				
SABA canisters per year				
0	0.38 (0.34–0.43)	<0.0001	0.64 (0.56–0.75)	<0.0001
1–2	1.00	(Reference)	1.00	(Reference)
3–5	1.73 (1.52–1.97)	<0.0001	1.59 (1.4–1.82)	<0.0001
⩾6	2.50 (2.17–2.87)	<0.0001	2.26 (1.96–2.60)	<0.0001
Covariate				
Deprivation quintile				
1 (least)	1.00	(Reference)	1.00	(Reference)
2	1.07 (0.91–1.25)	0.4335	1.05 (0.89–1.23)	0.5702
3	1.21 (1.03–1.41)	0.0185	1.14 (0.97–1.33)	0.1055
4	1.32 (1.14–1.54)	0.0003	1.23 (1.05–1.43)	0.0089
5 (most)	1.51 (1.30–1.76)	<0.0001	1.42 (1.22–1.65)	<0.0001
Dependency quintile				
1 (least)	1.00	(Reference)	1.00	(Reference)
2	0.82 (0.70–0.96)	0.0135	0.84 (0.71–0.98)	0.0305
3	0.99 (0.85–1.15)	0.8407	1.01 (0.87–1.18)	0.911
4	0.93 (0.8–1.09)	0.3596	0.95 (0.82–1.12)	0.558
5 (most)	0.89 (0.77–1.02)	0.0958	0.90 (0.78–1.05)	0.179
Age group at index date	0.98 (0.97–0.99)	<0.0001	0.98 (0.97–0.99)	<0.0001
Male sex (reference=female)	0.67 (0.60–0.75)	<0.0001	0.69 (0.62–0.77)	<0.0001
Rural residence (reference=urban)	1.67 (1.47–1.91)	<0.0001	1.73 (1.51–1.98)	<0.0001
Number of comorbidities				
0	1.00	(Reference)	1.00	(Reference)
1	1.01 (0.89–1.14)	0.8902	0.98 (0.86–1.11)	0.7211
2	1.05 (0.91–1.20)	0.5219	1.03 (0.90–1.19)	0.637
⩾3	0.91 (0.77–1.07)	0.2566	0.97 (0.82–1.15)	0.7115

AHR: adjusted hazard ratio; SABA: short-acting β_2-agonist.

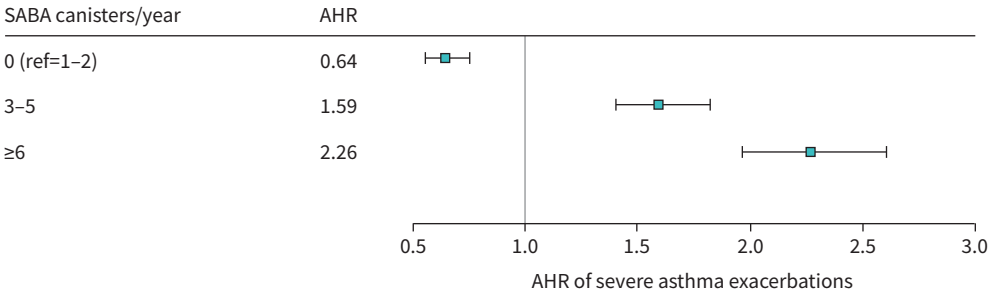

FIGURE 2 Forest plot comparing adjusted hazard ratios (AHRs) for severe asthma exacerbations from Cox proportional hazards regression. The Cox proportional hazards regression models were adjusted for the following: age, sex, prevalence of comorbidities, prevalence of asthma exacerbation at baseline as an indicator of severity of asthma, Ontario Marginalization Index (deprivation and dependency), rurality and asthma medication use at baseline. SABA: short-acting β_2-agonist; ref: reference.

and the UK [9]. For example, Nwaru *et al*. [7] used the Swedish national registries data from 2006 to 2014 in asthma patients aged 12–45 years and reported that increasing number of collected SABA canisters was associated with increased risk of asthma exacerbations. The estimated increased HRs were 1.26, 1.44 and 1.77 in those who used 3–5, 6–10 and ⩾11 SABA canisters per year, respectively. The study also showed that higher SABA use was associated with incrementally increased mortality risk with an over two-fold risk in those who used ⩾11 SABA canisters annually [7]. In Italy, the 2-year follow-up study using the Longitudinal Patient Database that included over 22 000 patients found that SABA overuse was common with an average of 4 SABA canisters purchased annually [8]. The study found that the use of >2 SABA canisters per year was associated with nearly 30% higher likelihood of experiencing exacerbations (HR=1.27, 95% CI: 1.21–1.33) [8]. Similarly, in the UK, amongst the 336 412 patients with linked hospital data, high SABA inhaler use was found to have a significantly increased risk of exacerbations (HR=1.24, 95% CI: 1.20–1.28) and asthma-related hospital outpatient HSU (HR=1.19, 95% CI: 1.13–1.26) [9].

Outside Europe, Wang *et al*. [23] used data from the Taiwanese pay-for-performance asthma programme database to investigate the prevalence of SABA overuse in the asthma population and the associated risk of acute exacerbation and mortality in Taiwan. The study included 218 039 patients aged 12–100 years who were enrolled in the programme from 2001 to 2015 and nearly 16% of these patients were classified as SABA over-users. Among users of ⩾3 SABA canisters per year, the study found statistically significant higher risks of SAEx (HRs ranged from 2.43 to 4.94 for 3–6 and >6 SABA canisters, respectively) and significantly higher risks of all-cause mortality (HRs ranged from 1.17 to 2.01 for 3–6 and >6 SABA canisters, respectively), compared with patients who used ⩽2 SABA canisters.

In Ontario, the rate of SABA overuse was approximately 14% in those ⩾65 years of age. While this rate was lower than reported in Europe and Taiwan, note that our population was older than populations in those studies. After adjusting for important potential confounders, including comorbidities, baseline asthma severity and baseline ICS use, our study quantified the associations of incremental use of SABA and the risks in SAEx and death. Our findings are amplified by other global publications with >1 million asthma patients and directionally similar findings. There is no place for clinical complacency regarding the impact of high SABA use.

While we reported associations between SABA therapy and adverse health outcomes, we do not infer causality. It may be that the high use of SABA is associated with other factors that can destabilise asthma, like low adherence to ICS. As an exploration of causation one can consider the six attributes of causal inference methodology [24, 25]:

1) “Experimental evidence and natural experiments” – the strong connection between the introduction of fenoterol and the epidemic of asthma deaths in New Zealand [4] along with the recent randomised controlled trial evidence that SABA *p.r.n.* had a higher SAEx rate than ICS-formoterol [26].
2) “Consistency” – this study is the third large modern international observational study that connects SABA use to death [7, 23] and the fifth connecting SABA with SAEx in separate jurisdictions [7–9, 23]. The modern studies confirm findings from the historical literature [5].
3) “Strength of the observed association” – large precise HRs across the studies [7–9, 23].

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TABLE 4 Summary of findings from other published studies

Country	Authors [ref.]	Published year	Journal	Year of data	Study population	Study size	Findings		
							SABA overuse prevalence (%)	All-cause mortality[#]	Asthma exacerbation[#]
France	Raherison-Semjen *et al.* [21]	2018	*Eur Respir J*	2018	Aged ⩾18 years with an asthma diagnosis	n=15 587	28.30	Not reported	Not reported
Poland	Kupczyk *et al.* [22]	2019	*Eur Respir J*	2018	Aged 18–64 years with an asthma diagnosis	n=91 673	29–37	Not reported	Not reported
Germany	Worth *et al.* [19]	2021	*Respir Res*	2017–2018	Aged ⩾12 years with an asthma diagnosis in the Disease Analyser database (IQVIA)	n=15 640	36	Not reported	Not reported
UK	Bloom *et al.* [9]	2020	*Adv Ther*	2007–2017	Aged ⩾12 years with an asthma diagnosis	n=574 913	38	Not available (due to small numbers)	1–2 canisters: 1.20 (1.16–1.24) 3–5 canisters: 1.24 (1.20–1.28)
Italy	Di Marco *et al.* [8]	2021	*Adv Ther*	2015–2018	Aged ⩾12 years with an asthma diagnosis	n=22 102	9	Not reported	Compared to <3 canisters/year: ⩾3 canisters: 1.27 (1.21–1.33)
Sweden	Nwaru *et al.* [7]	2020	*Eur Respir J*	2006–2016	Aged 12–45 years in the nationwide longitudinal cohort, those who collected medication for COPD	n=365 324	30	Compared to <3 canisters/year: 3–5 canisters: 1.26 (1.14–1.39) 6–10 canisters 1.67 (1.49–1.87) ⩾11 canisters: 2.35 (2.02–2.72)	Compared to <3 canisters/year: 3–5 canisters: 1.26 (1.24–1.28) 6–10 canisters: 1.44 (1.41–1.46) ⩾11 canisters: 1.77 (1.72–1.83)
Taiwan	Wang *et al.* [23]	2021	*NPJ Prim Care Resp Med*	2001–2015	Aged 12–100 years with asthma who enrolled in the Taiwanese pay-for-performance asthma programme	n=218 039	16	Compared to no ICS and <3 canisters/year: 3–6 canisters: 1.17 (1.09–1.25) ⩾7 canisters: 2.01 (1.89–2.13)	Compared to no ICS and <3 canisters/year: 3–6 canisters: 2.43 (2.36–2.50) ⩾7 canisters: 4.94 (4.79–5.09)
Canada	To *et al.* (current study)	2022	*ERJ Open Res*	2006–2020	Aged 65–99 years with prevalent asthma in the OASIS	n=59 533	14	Compared to 1–2 canisters/year: 3–5 canisters: 1.11 (1.02–1.22) ⩾6 canisters: 1.56 (1.41–1.71)	Compared to 1–2 canisters/year: 3–5 canisters: 1.59 (1.40–1.82) ⩾6 canisters: 2.26 (1.96–2.60)

SABA: short-term β_2-agonist; ICS: inhaled corticosteroid; OASIS: Ontario Asthma Surveillance System. [#]: all-cause mortality and asthma exacerbation data presented as hazard ratio (95% CI).

4) "Biological Gradient" – there is a relationship between the level of exposure and the HR outcome [7–9, 23].
5) "Biological Plausibility" – evidence that regular SABA use results in tolerance to its bronchodilator and non-bronchodilator effects [3–7, 27, 28].
6) "Coherence" – multiple lines of evidence that support a cause-and-effect determination [4, 5, 7–9, 23, 26, 27].

The results from this study add to a body of literature that clinicians may consider as they examine the new asthma therapeutic paradigms recommended by GINA and other asthma bodies.

There are several limitations to this study. First, we were unable to assess true medication use from pharmacy claims data alone, thus estimates of SABA dose may not correspond to exact doses taken by individuals. Further, our study population was restricted to those aged ⩾65 years, all of whom were eligible for provincial drug plan coverage. This may limit the findings' generalisability, especially to a younger population. Health administrative data did not allow us to assess individual-level clinical risk factors that are associated with mortality risk, like severity of asthma with pulmonary functions, eosinophil counts and/or other biomarkers [29], asthma control [30, 31] and systemic inflammation [32]. However, we used proxy measures of baseline asthma severity including baseline severe asthma exacerbations and baseline use of asthma medications to adjust for asthma severity in our model. The strengths of population-based data are that they allowed for complete participant follow-up, a large sample size and high power, which was needed to detect an effect on a rare outcome, like death.

This is the first contemporary Canadian population-based study in older individuals, with findings outside of Europe, that demonstrated significantly increased risks of all-cause mortality and SAEx associated with SABA overuse. Our results are consistent with those previously reported by others. Clinicians can consider the safety risks of high SABA use in their patients and assess new treatment recommendations in the context of this evidence.

Provenance: Submitted article, peer reviewed.

Author contributions: T. To initiated and designed the study, interpreted findings and drafted the manuscript. J. Zhu conducted all statistical analysis, interpreted findings and acquired data. E. Terebessy revised the manuscript, created tables and figures, conducted a search of the literature and summarised literature findings, and acquired data. K. Zhang conducted a search of the literature and summarised literature findings. A.S. Gershon and C. Licskai interpreted findings. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest: T. To reports support for the present manuscript received from Ontario Ministry of Health to the Ontario Asthma Surveillance Information System allowed access to and processing of provincial administrative databases for this study. C. Licskai reports receiving grants or contracts from Novartis, Ontario Ministry of Health, Canadian Institutes of Health Research, Federal Economic Development Agency for Southern Ontario, Academic Medical Organization of Southwestern Ontario, AstraZeneca and Pfizer, outside the submitted work; payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events received from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim and Novartis, outside the submitted work; participation on a data safety monitoring board or advisory board for GlaxoSmithKline (advisory board on asthma biologics), AstraZeneca (global advisory board on asthma biologics), Sanofi Genzyme (asthma biologics advisory board), Teva Canada (Inhalation Advisory Board) and Novartis (Inhalation Asthma Advisory Board), outside the submitted work; and unpaid leadership or fiduciary roles in other boards, societies, committees or advocacy groups for Canadian Thoracic Society (Chair of the Asthma Assembly), Chair Canadian Respiratory Guidelines committee and Asthma Research Group, outside the submitted work. The remaining authors have nothing to disclose.

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