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Is Overreliance on SABA 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], Christopher Licskai[6,7]

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

Corresponding Author: Teresa To, Child Health Evaluative Sciences, Peter Gilgan Centre for Research and Learning, The Hospital for Sick Children, 686 Bay St, Toronto ON, M5G 0A4, 416-813-8498, teresa.to@sickkids.ca.

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Author Contributions: TT initiated and designed the study, interpreted findings, and drafted the manuscript. JZ conducted all statistical analysis, interpreted findings, and acquired data. ET revised the manuscript, created tables and figures, conducted a search of the literature and summarized literature findings, and acquired data. KZ conducted a search of the literature and summarized literature findings. AG and CL interpreted findings. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Take Home Message: Our 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.

Abstract

Recent Global Initiative for Asthma (GINA) recommendations reduce the role of short-acting beta-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 (HR) with 95% confidence intervals (CI) 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, 1/7 individuals with asthma overused SABA associated with an increased risk of severe asthma exacerbations and death. The adverse impacts of SABA overuse continue 30 years after early publications.

Abstract Word Count: 249

Keywords: Asthma, Inhaled corticosteroids, Short-acting beta-agonist, All-cause mortality, Causal inference

Introduction

Short-acting beta-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 signaled a shift toward the use of ICS whenever bronchodilators were required. Maintenance and reliever therapy serves to reduce severe exacerbations compared to a SABA prn 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 prn (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 added observational data in 1992 defining an association between SABA use, near-fatal asthma, death, and further defined a dose response.[5] 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 two-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 hospitalization, and outpatient health services use (HSU).[9]

There are a small but growing number of modern population-based studies quantifying the association between SABA overreliance and adverse outcomes. Observational data is 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 hospitalization 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 & 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 old with prevalent asthma in the decade between April 1, 2006 and March 31, 2015. Asthma diagnosis was determined based on an administrative case definition of ≥1 hospitalization for asthma, or ≥2 outpatient visits for asthma in two 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 Table E1) between April 1, 2006 and March 31, 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 nor asthma HSU. Public drug coverage is available through the Ontario Drug Benefit (ODB) program for those aged 65 years and older, and those registered in social assistance programs, along with their dependents.

Exclusion criteria: The study cohort was linked to the Ontario population-based chronic obstructive pulmonary disease (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 & Outcome Definitions

The primary exposure was the number of SABA canisters filled (see complete list in Table E1 including drug names). Baseline exposure to SABA was categorized based on SABA usage during the one 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 March 31, 2021, whichever occurs first. The cohort was followed from exposure for a maximum of five years or till March 31, 2021 to ascertain outcomes. The primary outcome was all-cause mortality

and 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, ON-Marg (deprivation and dependency], rurality, and asthma medication use at baseline. *Socioeconomic status* (SES) was measured by proxy, using the Ontario Marginalization Index (ON-Marg).[12] ON-Marg provided a measure of marginalization 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 marginalized) to 5 (most marginalized) for each dimension. *Residence* was rural if the individual resided in a community with ≤10,000 people, or urban if otherwise true. Baseline use of *asthma medication* was from usage during the one year post the index date. Asthma medications were grouped into combinations of inhaled corticosteroids (ICS), ICS combined with long-acting beta-agonist (LABA), short-acting beta-agonist (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, ischemic heart disease, acute myocardial infarction; see ICD-10-CA codes in 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-square statistics for categorial variables and ANOVA (analysis of variance) 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 (HR) 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% confidence intervals (CI) 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 old with prevalent asthma between April 1, 2006 and March 31, 2015. Of these, 8,465 (14.2%) filled ≥3 SABA canisters at baseline. During the five-year follow-up, a total of 7,684 (12.9%) died of all-causes and 1,726 (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, ≥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.

All-cause Mortality

During the five-year follow-up, 7,684 (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 utilization. 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, 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 five-year follow-up, there were 1,726 (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 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.

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] and the UK.[9] For example, Nwaru et al. used the Swedish national registries data from 2006-2014 in asthma patients aged 12-45 years and reported that increasing number of collected SABA canisters was associated with increased risk of asthma exacerbations.[7] The estimated HRs increased from 1.26, 1.44, to 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 2-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 four 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 health services use (HR=1.19, 95% CI: 1.13-1.26).[9]

Outside Europe, Wang et al. used data from the Taiwanese pay-for-performance asthma program database to investigate the prevalence of SABA overuse in the asthma population and the associated risk of acute exacerbation and mortality in Taiwan.[23] The study included 218,039 patients aged 12-100 years who were enrolled in the program from 2001-2015 and nearly 16% of these patients were classified as SABA over-users. Among users of ≥3 SABA canister 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 SABA 3-6 and >6 canisters, respectively), compared with patients who used ≤2 SABA canisters.

In Ontario, the rate of SABA overuse was approximately 14% in those ≥65 years. 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 more than 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 destabilize 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 randomized controlled trial

evidence that SABA prn 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] 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] and 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' generalizability, 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 it 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.

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References

1. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of Inhaled Corticosteroids and Long-Acting β-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. *Jama* 2018: 319(14): 1485-1496.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2019.
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2021.
4. Pearce N, Hensley MJ. Epidemiologic studies of beta agonists and asthma deaths. *Epidemiol Rev* 1998: 20(2): 173-186.
5. Spitzer WO, Suissa S, Ernst P, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992: 326(8): 501-506.
6. Janson C, Menzies-Gow A, Nan C, et al. SABINA: An Overview of Short-Acting β(2)-Agonist Use in Asthma in European Countries. *Adv Ther* 2020: 37(3): 1124-1135.
7. Nwaru BI, Ekström M, Hasvold P, et al. Overuse of short-acting β(2)-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J* 2020: 55(4).
8. Di Marco F, D'Amato M, Lombardo FP, et al. The Burden of Short-Acting β(2)-Agonist Use in Asthma: Is There an Italian Case? An Update from SABINA Program. *Adv Ther* 2021.
9. Bloom CI, Cabrera C, Arnetorp S, et al. Asthma-Related Health Outcomes Associated with Short-Acting β(2)-Agonist Inhaler Use: An Observational UK Study as Part of the SABINA Global Program. *Adv Ther* 2020: 37(10): 4190-4208.

10. Gershon AS, Wang C Fau - Guan J, Guan J Fau - Vasilevska-Ristovska J, et al. Identifying patients with physician-diagnosed asthma in health administrative databases. *Can Respir J* 2009: 16(6): 183-188.
11. Gershon AS, Wang C, Guan J, et al. Identifying individuals with physcian diagnosed COPD in health administrative databases. *Copd* 2009: 6(5): 388-394.
12. Matheson FI, Dunn JR, Smith KLW, et al. On-Marg Ontario Marginalization Index User Guide. Toronto: Centre for Research on Inner City Health; 2006.
13. Kleinbaum DG, Klein M. The Stratified Cox Procedure. *In:* Kleinbaum DG, Klein M, eds. Survival Analysis: A Self-Learning Text. Springer New York, New York, NY, 2012; pp. 201-240.
14. Busse PJ, McDonald VM, Wisnivesky JP, et al. Asthma Across the Ages: Adults. *J Allergy Clin Immunol Pract* 2020: 8(6): 1828-1838.
15. Gonzalez-Barcala FJ, Aboal J, Carreira JM, et al. Trends of asthma mortality in Galicia from 1993 to 2007. *J Asthma* 2012: 49(10): 1016-1020.
16. Kaplan A, Mitchell PD, Cave AJ, et al. Effective Asthma Management: Is It Time to Let the AIR out of SABA? *J Clin Med* 2020: 9(4).
17. Kaplan AG, Correia-de-Sousa J, McIvor A. Global Quality Statements on Reliever Use in Asthma in Adults and Children Older than 5 Years of Age. *Adv Ther* 2021: 38(3): 1382-1396.
18. Tupper OD, Andersen ZJ, Ulrik CS. Demographic, lifestyle and comorbid risk factors for all-cause mortality in a Danish cohort of middle-aged adults with incident asthma. *BMJ Open* 2021: 11(10): e049243.

19. Worth H, Criée CP, Vogelmeier CF, et al. Prevalence of overuse of short-acting beta-2 agonists (SABA) and associated factors among patients with asthma in Germany. *Respir Res* 2021: 22(1): 108.
20. Portel L, Parrat E, Nocent-Ejnaini C, et al. FASE-CPHG study: a panoramic snapshot of difficult-to-treat, severe asthma in French nonacademic hospitals. *ERJ Open Res* 2019: 5(4).
21. Raherison-Semjen C, Izadifar A, Russier M, et al. Late Breaking Abstract - Asthma prevalence and management in adults in France in 2018: ASTHMAPOP survey. *European Respiratory Journal* 2018: 52(suppl 62): OA292.
22. Kupczyk M, Barg W, Bochenek G, et al. Late Breaking Abstract - Overprescription of short-acting beta2-agonists in asthma management? Pharmacy reports from 91,673 patients in Poland. *European Respiratory Journal* 2019: 54(suppl 63): OA2107.
23. Wang CY, Lai CC, Wang YH, et al. The prevalence and outcome of short-acting β2-agonists overuse in asthma patients in Taiwan. *NPJ Prim Care Respir Med* 2021: 31(1): 19.
24. Agency USEP. Preamble to the Integrated Science Assessments. *In:* Standards. OoAQPa, ed., Research Triangle Park, NC, 2015.
25. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965: 58(5): 295-300.
26. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *N Engl J Med* 2018: 378(20): 1865-1876.
27. Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. *Ann Intern Med* 2004: 140(10): 802-813.
28. Hancox RJ. Concluding remarks: can we explain the association of beta-agonists with asthma mortality? A hypothesis. *Clin Rev Allergy Immunol* 2006: 31(2-3): 279-288.

29. Yii ACA, Tay TR, Puah SH, et al. Blood eosinophil count correlates with severity of respiratory failure in life-threatening asthma and predicts risk of subsequent exacerbations. *Clin Exp Allergy* 2019: 49(12): 1578-1586.
30. Gleadhill C, Speth MM, Gengler I, et al. Chronic rhinosinusitis disease burden is associated with asthma-related emergency department usage. *Eur Arch Otorhinolaryngol* 2021: 278(1): 93-99.
31. Cajigal S, Wells KE, Peterson EL, et al. Predictive Properties of the Asthma Control Test and Its Component Questions for Severe Asthma Exacerbations. *J Allergy Clin Immunol Pract* 2017: 5(1): 121-127 e122.
32. Benz E, Wijnant SRA, Trajanoska K, et al. Sarcopenia, systemic immune-inflammation index and all-cause mortality in middle-aged and older people with COPD and asthma: a population-based study. *ERJ Open Res* 2022: 8(1).

Table 1. Characteristics of the study population and baseline medication use by SABA canisters (N=59,533).

Number of SABA† Canisters		**0**	**1-2**	**3-5**	**≥6**	**Total**	
Covariates		**N=33,332**	**N=17,736**	**N=5,332**	**N=3,133**	**N=59,533**	***P* value***
Participant Factors							
Sex	Female	21,898 (65.7%)	12,561 (70.8%)	3,645 (68.4%)	1,982 (63.3%)	40,086 (67.3%)	<0.001
	Male	11,434 (34.3%)	5,175 (29.2%)	1,687 (31.6%)	1,151 (36.7%)	19,447 (32.7%)	
Age at index date	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	65-69	21,254 (63.8%)	11,551 (65.1%)	3,536 (66.3%)	2,080 (66.4%)	38,421 (64.5%)	<0.001
	70-74	5,533 (16.6%)	3,044 (17.2%)	841 (15.8%)	476 (15.2%)	9,894 (16.6%)	
	75-79	3,415 (10.2%)	1,727 (9.7%)	498 (9.3%)	300 (9.6%)	5,940 (10.0%)	
	80-89	3,130 (9.4%)	1,414 (8.0%)	457 (8.6%)	277 (8.8%)	5,278 (8.9%)	
Age at asthma prevalence	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
	Mean ± SD	10.03 ± 6.61	10.12 ± 6.85	9.32 ± 7.07	9.60 ± 7.09	9.97 ± 6.76	<0.001

Years of asthma at index date	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							
	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%)	3,988 (22.5%)	1,742 (32.7%)	1,134 (36.2%)	18,517 (31.1%)	
	SABA[†] only	0 (0.0%)	6,292 (35.5%)	1,100 (20.6%)	491 (15.7%)	7,883 (13.2%)	
	Other asthma medications	1,007 (3.0%)	7,456 (42.0%)	2,490 (46.7%)	1,508 (48.1%)	12,461 (20.9%)	
Socio-Demographic Factors							
Neighbourhood Income Quintile	1 (Lowest)	5,639 (16.9%)	2,972 (16.8%)	1,051 (19.7%)	704 (22.5%)	10,366 (17.4%)	<0.001
	2	6,648 (19.9%)	3,562 (20.1%)	1,133 (21.2%)	726 (23.2%)	12,069 (20.3%)	
	3	6,445 (19.3%)	3,563 (20.1%)	1,073 (20.1%)	642 (20.5%)	11,723 (19.7%)	
	4	6,911 (20.7%)	3,763 (21.2%)	1,048 (19.7%)	522 (16.7%)	12,244 (20.6%)	
	5 (Highest)	7,604 (22.8%)	3,843 (21.7%)	1,010 (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 marginalized)							
Deprivation Quintile	1 (Least)	6,953 (20.9%)	3,735 (21.1%)	1,000 (18.8%)	516 (16.5%)	12,204 (20.5%)	<0.001

	2	6,752 (20.3%)	3,517 (19.8%)	978 (18.3%)	505 (16.1%)	11,752 (19.7%)	
	3	6,606 (19.8%)	3,506 (19.8%)	989 (18.5%)	616 (19.7%)	11,717 (19.7%)	
	4	6,652 (20.0%)	3,532 (19.9%)	1,190 (22.3%)	710 (22.7%)	12,084 (20.3%)	
	5 (Most)	6,185 (18.6%)	3,354 (18.9%)	1,135 (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	1 (Least)	5,449 (16.3%)	3,186 (18.0%)	1,044 (19.6%)	678 (21.6%)	10,357 (17.4%)	<0.001
	2	5,981 (17.9%)	3,322 (18.7%)	1,040 (19.5%)	620 (19.8%)	10,963 (18.4%)	
	3	6,142 (18.4%)	3,236 (18.2%)	971 (18.2%)	611 (19.5%)	10,960 (18.4%)	
	4	6,528 (19.6%)	3,326 (18.8%)	937 (17.6%)	512 (16.3%)	11,303 (19.0%)	
	5 (Most)	9,048 (27.1%)	4,574 (25.8%)	1,300 (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%)	
Ethnic Concentration Quintile	1 (Least)	5,161 (15.5%)	2,846 (16.0%)	830 (15.6%)	461 (14.7%)	9,298 (15.6%)	<0.001
	2	5,325 (16.0%)	2,928 (16.5%)	856 (16.1%)	418 (13.3%)	9,527 (16.0%)	
	3	6,005 (18.0%)	3,135 (17.7%)	848 (15.9%)	455 (14.5%)	10,443 (17.5%)	
	4	7,207 (21.6%)	3,567 (20.1%)	960 (18.0%)	560 (17.9%)	12,294 (20.7%)	
	5 (Most)	9,450 (28.4%)	5,168 (29.1%)	1,798 (33.7%)	1,219 (38.9%)	17,635 (29.6%)	

	Missing	184 (0.6%)	92 (0.5%)	40 (0.8%)	20 (0.6%)	336 (0.6%)	
Instability Quintile	1 (Least)	6,470 (19.4%)	3,689 (20.8%)	1,129 (21.2%)	712 (22.7%)	12,000 (20.2%)	<0.001
	2	6,539 (19.6%)	3,512 (19.8%)	949 (17.8%)	516 (16.5%)	11,516 (19.3%)	
	3	6,224 (18.7%)	3,264 (18.4%)	975 (18.3%)	560 (17.9%)	11,023 (18.5%)	
	4	6,045 (18.1%)	3,188 (18.0%)	1,017 (19.1%)	535 (17.1%)	10,785 (18.1%)	
	5 (Most)	7,870 (23.6%)	3,991 (22.5%)	1,222 (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		3,046 (9.1%)	1,738 (9.8%)	545 (10.2%)	307 (9.8%)	5,636 (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	0	7,732 (23.2%)	4,029 (22.7%)	1,206 (22.6%)	626 (20.0%)	13,593 (22.8%)	0.001
	1	12,762 (38.3%)	6,940 (39.1%)	2,053 (38.5%)	1,240 (39.6%)	22,995 (38.6%)	
	2	8,260 (24.8%)	4,407 (24.8%)	1,396 (26.2%)	831 (26.5%)	14,894 (25.0%)	
	≥3	4,578 (13.7%)	2,360 (13.3%)	677 (12.7%)	436 (13.9%)	8,051 (13.5%)	
Outcomes							
Deaths		4,487 (13.5%)	1,942 (10.9%)	703 (13.2%)	552 (17.6%)	7,684 (12.9%)	<0.001

Severe asthma exacerbation	446 (1.3%)	642 (3.6%)	343 (6.4%)	295 (9.4%)	1,726 (2.9%)	<0.001

[*] *P* values were calculated using Chi-square statistics for categorical variables and ANOVA for numeric variables

[†] short-acting beta-agonist

[‡] inhaled corticosteroid

[§] inhaled corticosteroid-long-acting beta-agonist

Table 2. All-cause mortality hazard ratios from Cox-Proportional hazard regressions (N=59,533).

		HR*	95% confidence interval	*P* value	AHR†	95% confidence interval	*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
Sex *(ref=Female)*	Male	1.09	(1.04 - 1.14)	0.00	1.30	(1.24 - 1.36)	<0.0001
Rural residence *(ref=Urban)*	Yes	1.05	(0.97 - 1.13)	0.24	1.19	(1.10 - 1.28)	<0.0001

Asthma medication use in baseline period													
ICS[§] only or ICS-LABA[ll]		1.00			(Reference)			1.00			(Reference)		
No asthma medications		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 medications		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

[*] hazard ratio (unadjusted)

[†] adjusted hazard ratio

‡ short-acting beta-agonist

[§] inhaled corticosteroid

[ll] inhaled corticosteroid-long-acting beta-agonist

Table 3. Severe asthma exacerbation hazard ratios from Cox-Proportional hazard regressions (N=59,533).

		HR*	95% confidence interval	*P* value	AHR†	95% confidence interval	*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
Sex *(ref=Female)*	Male	0.67	(0.60 - 0.75)	<.0001	0.69	(0.62 - 0.77)	<0.0001

Rural residence (ref=Urban)	Yes	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

* hazard ratio (unadjusted)

† adjusted hazard ratio

‡ short-acting beta-agonist

Table 4. Summary of findings from other published studies.

							Findings	
Country	**Authors**	**Published year**	**Journal**	**Year of data**	**Study population**	**Study size**	**SABA* overuse prevalence**	**All-cause mortality**	**Asthma exacerbation**
France	Raherison-Semjen et al.[16]	2018	ERJ	2018	aged ≥18 year with an asthma diagnosis	N=15,587	28.30%	Not reported	Not reported
Poland	Kupczyk et al.[17]	2019	ERJ	2018	aged 18-64 years with an asthma diagnosis	N=91,673	29-37%	Not reported	Not reported
Germany	Worth et al.[14]	2021	Respir Res	2017-2018	aged ≥12 year with an asthma diagnosis in the Disease Analyzer database (IQVIA)	N=15,640	36%	Not reported	Not reported
UK	Bloom et al.[9]	2020	Adv Ther	2007-2017	aged ≥12 year with an asthma diagnosis	N=574,913	38%	Not available (due to small numbers)	1-2 canisters: HR‡=1.20 (1.16-1.24) 3-5 canisters: HR‡=1.24 (1.20-1.28)
Italy	Di Marco et al.[8]	2021	Adv Ther	2015-2018	aged ≥12 year with an asthma diagnosis	N=22,102	9%	Not reported	compared to <3 canisters/year: ≥3 canisters: HR‡=1.27 (1.21–1.33)
Sweden	Nwaru et al.[7]	2020	ERJ	2006-2016	aged 12-45 year in the Nationwide longitudinal cohort, those who collected	N=365,324	30%	compared to <3 canisters/year: 3–5 canisters: HR‡ 1.26 (1.14–1.39) 6–10 canisters HR‡=1.67 (1.49–1.87)	compared to <3 canisters/year: 3–5 canisters: HR‡=1.26 (1.24–1.28) 6–10 canisters: HR‡=1.44 (1.41–1.46)

					medications for COPD[†]			≥11 canisters: HR[‡]=2.35 (2.02–2.72)	≥11 canisters: HR[‡]=1.77 (1.72–1.83)
Taiwan	Wang et al.[18]	2021	NPJ Pri Care Resp Med	2001-2015	aged 12-100 year with asthma who enrolled in the Taiwanese pay-for-performance asthma program	N=218,039	16%	compared to no ICS[§] and <3 canisters/year: 3-6 canisters: HR[‡]=1.17 (1.09-1.25) ≥7 canisters: HR[‡]=2.01 (1.89-2.13)	compared to no ICS[§] and <3 canisters/year: 3-6 canisters: HR[‡]=2.43 (2.36-2.50) ≥7 canisters: HR[‡]=4.94 (4.79-5.09)
Canada	To et al. (current study)	2022	ERJ Open Res (submitted)	2006-2020	aged 65-99 year with prevalent asthma in the Ontario Asthma Surveillance System (OASIS)	N=59,533	14%	compared to 1-2 canisters/year: 3–5 canisters: HR[‡]=1.11 (1.02–1.22) ≥6 canisters: HR[‡]=1.56 (1.41-1.71)	compared to 1-2 canisters/year: 3–5 canisters: HR[‡]=1.59 (1.40–1.82) ≥6 canisters: HR[‡]=2.26 (1.96-2.60)

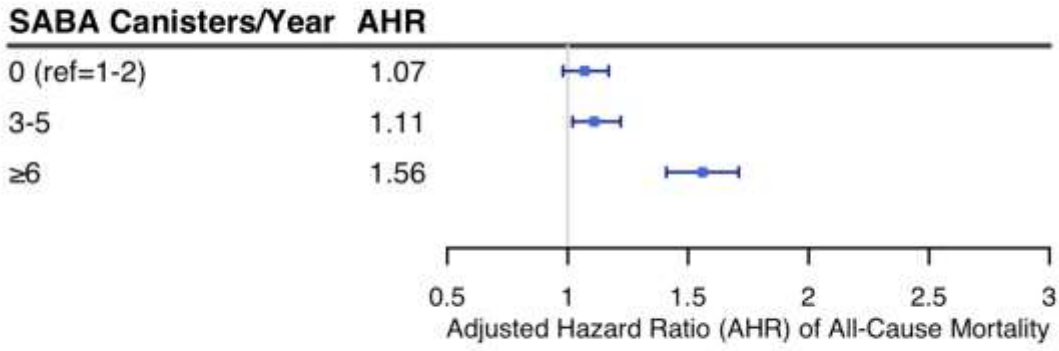
[*] short-term beta-agonist

[†] chronic obstructive pulmonary disease

[‡] hazard ratio

[§] inhaled corticosteroid

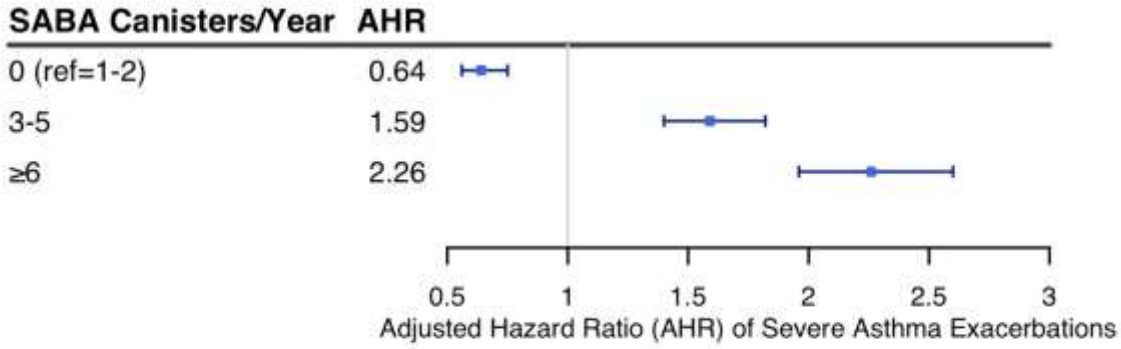
Figure 1. Forest plot comparing adjusted hazard ratios for all-cause mortality from Cox-Proportional hazards regression.



1. AHR=adjusted hazard ratio.

2. 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.

Figure 2. Forest plot comparing adjusted hazard ratios for severe asthma exacerbations from Cox-Proportional hazards regression.



1. AHR=adjusted hazard ratio.

2. 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.

Is Overreliance on SABA Associated with Health Risks in the Older Asthma Population?

Teresa To, Jingqin Zhu, Emilie Terebessy, Kimball Zhang, Andrea S Gershon,
Christopher Licskai

Online Data Supplement

Table E1. List of asthma medications by category.

Drug Identification Number	Drug Name
Short-acting beta-agonist	
303569	albuterol
334227	albuterol sulfate
444774	terbutaline sulfate
622060	albuterol sulfate
622079	albuterol sulfate
667242	albuterol sulfate
786616	terbutaline sulfate
790419	albuterol
818739	terbutaline sulfate
832758	albuterol sulfate
832766	albuterol sulfate
851841	albuterol
860808	albuterol sulfate
867179	albuterol
874086	albuterol
897345	albuterol sulfate
1926934	albuterol sulfate
1938851	albuterol sulfate
1938878	albuterol sulfate
1945203	albuterol sulfate
1947222	albuterol sulfate
1986864	albuterol sulfate
2022125	albuterol sulfate
2046741	albuterol sulfate
2048760	albuterol sulfate
2053136	pirbuterol acetate
2069571	albuterol sulfate
2154412	albuterol sulfate
2173360	albuterol sulfate
2208229	albuterol sulfate
2208237	albuterol sulfate
2212315	albuterol sulfate
2212323	albuterol sulfate
2213419	albuterol sulfate
2213427	albuterol sulfate
2213478	albuterol

Table E1 – continued.

2213486	albuterol sulfate
2214997	albuterol sulfate
2215004	albuterol sulfate
2231430	albuterol sulfate
2231488	albuterol
2231678	albuterol sulfate
2232570	albuterol sulfate
2232987	albuterol sulfate
2239366	albuterol sulfate
2241497	albuterol sulfate
2244914	albuterol sulfate
2245669	albuterol sulfate
2326450	albuterol sulfate
Inhaled corticosteroid	
334243	beclomethasone dipropionate
374407	beclomethasone dipropionate
545325	beclomethasone dipropionate
545333	beclomethasone dipropionate
634549	budesonide
768707	beclomethasone dipropionate
769983	triamcinolone acetonide
790486	flunisolide
814091	budesonide
828521	beclomethasone dipropionate
828548	beclomethasone dipropionate
851752	budesonide
851760	budesonide
852074	budesonide
872334	beclomethasone dipropionate
893633	beclomethasone dipropionate
897353	beclomethasone dipropionate
1926314	triamcinolone acetonide
1949993	beclomethasone dipropionate
1950002	beclomethasone dipropionate
1978918	budesonide
1978926	budesonide
2174758	fluticasone propionate
2174766	fluticasone propionate
2174774	fluticasone propionate

Table E1 – continued.

2213591	fluticasone propionate
2213605	fluticasone propionate
2213613	fluticasone propionate
2213710	beclomethasone dipropionate
2213729	beclomethasone dipropionate
2215039	beclomethasone dipropionate
2215047	beclomethasone dipropionate
2215055	beclomethasone dipropionate
2216531	beclomethasone dipropionate
2229099	budesonide
2237245	fluticasone propionate
2237246	fluticasone propionate
2237247	fluticasone propionate
2242029	beclomethasone dipropionate
2242030	beclomethasone dipropionate
2243595	mometasone furoate
2243596	mometasone furoate
2244291	fluticasone propionate
2244292	fluticasone propionate
2244293	fluticasone propionate
2285606	ciclesonide
2285614	ciclesonide
2444186	fluticasone furoate & vilanterol triphenylacetate
2446561	fluticasone furoate
2446588	fluticasone furoate
9857431	mometasone furoate
9857672	beclomethasone dipropionate
9857673	beclomethasone dipropionate
9857675	budesonide
9857676	budesonide
9857677	budesonide
9857679	budesonide
9857680	budesonide
Inhaled corticosteroid-long-acting beta-agonist	
2240835	fluticasone propionate & salmeterol xinafoate
2240836	fluticasone propionate & salmeterol xinafoate
2240837	fluticasone propionate & salmeterol xinafoate
2245126	fluticasone propionate & salmeterol xinafoate
2245127	fluticasone propionate & salmeterol xinafoate

Table E1 – continued.

2245385	budesonide & formoterol fumarate
2245386	budesonide & formoterol fumarate
2408872	fluticasone furoate & vilanterol triphenylacetate
2418401	umeclidinium bromide & vilanterol triphenylacetate
Long-acting muscarinic	
2246793	tiotropium bromide
2394936	glycopyrrolate bromide
2423596	umeclidinium bromide
2435381	tiotropium bromide
Long-acting muscarinic-long-acting beta-agonist	
2409720	aclidinium bromide
2418282	glycopyrrolate bromide & indacaterol maleate
2439530	aclidinium & formoterol fumarate
Long-acting beta-agonist	
371807	fenoterol hbr
541389	fenoterol hbr
846414	procaterol hcl
2006383	fenoterol hbr
2056704	fenoterol hbr
2056712	fenoterol hbr
2136139	salmeterol xinafoate
2136147	salmeterol xinafoate
2211742	salmeterol xinafoate
2214261	salmeterol xinafoate
2230898	formoterol fumarate
2231129	salmeterol xinafoate
2237224	formoterol fumarate
2237225	formoterol fumarate
2361744	formoterol & mometasone
2361752	formoterol & mometasone
2361760	formoterol & mometasone
2376938	indacaterol maleate
Short-acting muscarinic	
576158	ipratropium bromide
731439	ipratropium bromide
1950681	ipratropium bromide
2026759	ipratropium bromide
2097141	ipratropium bromide
2097168	ipratropium bromide

Table E1 – continued.

2097176	ipratropium bromide
2126222	ipratropium bromide
2210479	ipratropium bromide
2216221	ipratropium bromide
2231135	ipratropium bromide
2231136	ipratropium bromide
2231245	ipratropium bromide
2231494	ipratropium bromide
2239131	ipratropium bromide
2243827	ipratropium bromide
2247686	ipratropium bromide
9857752	ipratropium bromide
9857754	ipratropium bromide
9857755	ipratropium bromide
Short-acting beta-agonist-short-acting muscarinic	
2163721	albuterol sulfate & ipratropium bromide
2231675	albuterol sulfate & ipratropium bromide
2243789	albuterol sulfate & ipratropium bromide
2266393	albuterol sulfate & ipratropium bromide
2272695	albuterol sulfate & ipratropium bromide

Table E2. List of comorbidities by ICD-10-CA code.

Comorbidity	ICD-10-CA* Code
Diabetes	E10, E11, E13, E14
Hypertension	I10, I11, I12, I13, I15
Angina	I20
Stroke	G45, G46, I63, I64
Acute myocardial infarction	I21

* ICD-10-CA=International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada.