Estimating Use of Short-term Asthma Reliever Inhalers from Electronic Prescription Records

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Abstract: Asthma is a common chronic lung disease which can be effectively managed for most people through regular use of inhaled controller therapy. Short-acting Beta-2 Agonists (symptom relievers; SABA) may also be prescribed to be used as needed, however over-reliance may indicate poor symptom control. SABA usage can be estimated from refill rate observed in prescribing records. This study was a secondary analysis of a Scottish longitudinal dataset of linked primary and secondary care data. The aims of this study were to estimate the mean inhaled SABA dose per day for people diagnosed with asthma in a large EHR database, and to examine variation by demographic factors such as age, sex, and social deprivation. The prescriptions dataset contained over 40 million prescriptions between 2009 and 2017. 1,987,119 asthma reliever prescription records were identified (5% of all prescriptions), of which 97% were inhaled formulations. The Spearman correlation coefficient between subsequent years of aggregated (median) daily estimated SABA from one person-year to the next was 0.67. Higher median daily inhaled SABA amounts were statistically significantly associated (Wilcoxon Rank-Sum test p-value<0.05) with being older, male, living in an area of higher deprivation, and any non-inhaled SABA prescription.

1 INTRODUCTION

Asthma is a common chronic lung disease characterised by inflammation of the airways and *hyper-responsiveness* (sensitivity of the nerve endings in the airways so they become easily irritated) to stimuli including allergens, exercise, and infections (World Health Organization, 2020). Inflammation results in obstruction of the airways, and can present as wheezing, chest tightness, coughing and shortness of breath (American Academy of Allergy Asthma & Immunology, 2020).

Asthma can be effectively managed for most people through regular use of Inhaled Cortico-Steroids (ICS) (Barnes, 1998; Barnes & Pedersen, 1993; Suissa, Ernst, Benayoun, Baltzan, & Cai, 2000), although additional therapies such as Long-Acting Muscarinic Antagonists (LAMA) and Monoclonal Antibody therapy (MAb) (British Thoracic Society & SIGN, 2019; Global Initiative for Asthma, 2019; Peters, Ferguson, Deniz, & Reisner, 2006) may be used in parallel for those with insufficient control of their symptoms. Additionally, most people are prescribed Short-Acting β-2 Agonist (SABA) symptom reliever inhalers to be used as needed (British Thoracic Society & SIGN, 2019; Global Initiative for Asthma, 2019). SABA is a *bronchodilator* (it opens the airways) which acts by relaxing the muscles in the airways, with effects lasting for around three to six hours (Ullman & Svedmyr, 1988).

SABA may also be prescribed at higher doses in non-inhaled formulations, including tablet, syrup, injections or using a nebuliser (Pharmaceutical Press Joint Formulary Committee, 2019a). Other reliever medications are also available, such as anticholinergics or theophylline (British Thoracic Society & SIGN, 2019; Global Initiative for Asthma,

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2019; Peters et al., 2006). These may be used in conjunction with controller medications, such as inhalers containing both an ICS and a Long-Acting β-2 Agonist (LABA), components (O'Byrne et al., 2018), as alternatives to SABA, or simply as additional reliever therapy.

While use of SABA inhalers is encouraged to relieve exacerbations, both mild and severe, regular usage is an indicator that current therapy is not sufficient to achieve symptom control. The 2021 Global INitiative for Asthma (GINA) guidelines classify SABA over-use as three or greater 200-dose SABA inhalers within a year (Reddel et al., 2021). Estimating an individual's SABA usage may flag when a step-up in therapy may be required, or when an individual is not sufficiently adherent to their routine controller therapy (Chan et al., 2020). This can be used identify those currently at higher risk of adverse outcomes, including the need for unscheduled care, morbidity, and mortality (Canonica et al., 2021; Stanford, Shah, D'Souza, Dhamane, & Schatz, 2012).

Electronic Health Records (EHRs) can be used in pragmatic observational and intervention studies of asthma (Varsano, Segev, & Shitrit, 2017). SABA usage can be estimated from prescribing records by recording the rate of SABA cannister refill. While previous studies have reported reliever use estimated from prescribing records, the methodology has not been sufficiently described for reproducibility or validated. For example, many studies measure SABA use averaged over a year (Blakey et al., 2017; Disantostefano, Boudiaf, Stempel, Barnes, & Greening, 2016; FitzGerald, Tavakoli, Lynd, Al Efraij, & Sadatsafavi, 2017; Lugogo et al., 2021; Makhinova, Barner, Richards, & Rascati, 2015; Stanford et al., 2012), however this leads to substantial delay in the detection of increased use.

The aims of this paper were to: (1) estimate the mean inhaled SABA dose per day for people diagnosed with asthma in a large EHR database, and (2) examine the trends of mean inhaled SABA dose with regards to consistency over time and variation by demographic factors such as age, sex, and social deprivation.

2 METHODS

2.1 Data

The Asthma Learning Healthcare System (ALHS) dataset was created to develop and validate a prototype *learning healthcare system* for asthma patients in Scotland, in which patient data are used to generate a continuous loop of knowledge-generation, evidence based clinical practice change, and change assessment/validation (Soyiri et al., 2018). Over half a million patients from 75 general practices in Scotland were recruited, with primary care records linked to national accident and emergency, hospital and mortality datasets using the Scottish health identification number known as the Community Health Index (CHI) (Tibble et al., 2019). The prescriptions dataset contained 41,432,295 valid prescription records for 671,298 individuals dated between January 31st, 2009, to March 31st, 2017.

2.2 Reliever Medication Processing

To identify asthma medications, the medication's name was searched for "SALBUTAMOL" or any of the brand names listed in Table 1 (extracted from the British National Formulary Version 80; September 2020 (Pharmaceutical Press Joint Formulary Committee, 2019a)).

Reliever medications with non-inhaled formulations (tablets, injections, or nebulising solution) were identified. For inhaled medications, the mean inhaled SABA dosage per day was estimated from the dosage, the quantity prescribed, and the dates between prescriptions.

The medication strength (micrograms of salbutamol in each dose unit, e.g., inhaler puff) was then extracted by searching the medication name for any of the values 95, 100, 200, or 400, followed by "MICRO" or "MCG" (with or without a preceding space). The volume of the inhaler was estimated by searching the medication name for 60, 100, 120, or 200, following by "DOSE" (with or without a preceding space or hyphen). The most common pack sizes per brand and strength were then examined so that the modal value could be imputed.

The 99.9th percentile of the dispensed quantity of inhalers in a single prescription was calculated to be used as the upper threshold for outliers, such as recording the prescription of a 200-dose inhaler mistakenly as the prescription of 200 inhalers. In such cases, the recorded quantity was replaced with the value 1 (a single inhaler).

Finally, multiple prescriptions of inhaled salbutamol collected on the same day (multiple prescriptions for single inhaler units rather than a single prescription for multiple units) were condensed into a single prescription.

Table 1: Salbutamol brand names, formulations, and strengths.

Brand Names	Formulation	Medication Strength
Generic	Tablet	2mg, 4mg
	Oral Solution	2mg/5ml
	Pressurised Inhaler	100mcg
	Inhalation Powder	100mcg, 200mcg
	Nebulising Solution	2.5mg/2.5ml, 5mg/2.5ml
Salamol	Pressurised Inhaler	100mcg
	Nebulising Solution	5mg/2.5ml
Ventolin	Infusion Ampoules	5mg/5ml
	Injection	500mcg/1ml
	Oral Solution	2mg/5ml
	Pressurised Inhaler	100mcg
	Inhalation Powder	200mcg
	Nebules	2.5mg, 5mg
	Nebulising Solution	5mg/1ml
Airomir	Pressurised Inhaler	100mcg
Salbulin	Inhalation Powder	100mcg
AirSalb	Pressurised Inhaler	100mcg
Ventmax	Capsule	4mg, 8mg
Asmasal	Inhalation Powder	95mcg
Pulvinal Salbutamol	Inhalation Powder	200mcg

2.3 Analysis Plan

The asthma reliever prescription record identification and cleaning process was reported. The number of inhaled SABA cannisters prescribed per person-year (in which at least one was prescribed) and time between prescriptions was summarised.

The mean SABA dosage daily was then estimated as the prescribed quantity of inhalers multiplied by the medication strength in micrograms and the volume of the inhaler unit, and then divided by the number of days until the next prescription.

The deviation in estimates of daily inhaled SABA usage by person and by person-year were estimated, and the Spearman correlation coefficient between an individual's average from one year to the next was evaluated.

The differences in inhaled SABA use associated with non-inhaled salbutamol use and demographic factors (age, sex, and deprivation) were investigated using Wilcoxon Rank Sum tests. For the non-binary variables (age and deprivation), increments of ordinal categories were assessed in a pairwise manner. The Scottish Index of Multiple Deprivation (SIMD) is a composite geographic-level measure incorporating income, employment, education, health, access to services, crime and housing (Scottish Government National Statistics Publications, 2016), reported here in quintiles.

3 RESULTS

3.1 Reliever Medication Identification

Of the 41,432,295 valid prescription records, 1,987,119 (4.8%) were identified as salbutamol products. 68,265 (3.4%) of the prescriptions were identified as relating to non-inhaled formulations. For 65.4%, no brand name was listed, indicating either that it was a generic, or that the recorded information was incomplete. 27.1% of records were for Ventolin, and the remaining 7.6% had other recorded brands.

1,918,854 of the prescriptions related to inhaled salbutamol, of which 79.4% were unbranded, 9.4% were Ventolin, 9.2% were Salamol, and 2.6% were Airomir (remaining 0.4% of prescriptions were for other brands). The most commonly prescribed strength was 100mcg (94.1% of prescriptions), followed by 200mcg (5.4%), 95mcg (0.5%), and 400mcg (<0.1%). Asmasal was the most common brand at 95mcg (44.5%), and 55.5% were generic. 100% of the 400mcg prescriptions were generic.

The number of doses per cannister was not recorded in the prescription data for 84.7% of prescriptions. Table 2 shows the most common number of doses that could be extracted from each brand and strength, the percentage of extractable records with that value, and the number of records for which no value was extractable.

Table 2: The most common doses per cannister extracted by brand name and strength from inhaled salbutamol prescriptions.

Brand	Strength (micrograms)	Doses per Cannister	Percentage of prescriptions with this value extracted	Percentage of prescriptions no value extractable
Generic / Brand not listed	95	200	100%	48.9%
	100	200	100%	84.9%
	200	60	64.8%	64.9%
	400	200	100%	98.1%
Airomir	100	200	100%	77.7%
Asmasal	95	200	99.8%	81.5%
Pulvinal	200	100	98.0%	89.0%
Salamol	100	200	100%	84.4%
Salbulin	100	200	100%	96.9%
Ventolin	100	200	100%	90.6%
	200	60	99.0%	89.8%

Consequently, Pulvinal was imputed as 100 doses, Ventolin and generic (or brand not listed) 200mcg as 60 doses, and all other brand-strengths as 200 doses. In total, 94.8% of prescriptions were estimated to have 200 doses, 4.9% to have 60 doses, and 0.3% to have 100 doses.

Less than 0.01% of records had missing quantity, and 0.07% had quantity above the calculated outlier threshold of 4 inhalers. After imputing these records to have a single unit quantity, the quantity of cannisters prescribed was estimated to be 1 for 50.1% of prescriptions, 2 for 48.5%, 3 for 0.8%, and 4 for 0.6%.

Finally, multiple prescriptions of single inhaled salbutamol cannisters collected on the same day were condensed into a single prescription, resulting in 1,882,586 person-days.

3.2 Inhaled Salbutamol Use

In years containing at least one inhaled SABA prescription, a median of 3 cannisters were obtained (range 1 – 262, interquartiles 1-6). This was equal to a median of 420 doses obtained each year (range 1-52400, interquartiles 200-1200). Using the GINA criteria (Reddel et al., 2021), a median of 66.7% of each individual's person-years could be classed as periods of over-use (range 11.1% - 100%, interquartiles 37.5% - 88.9%).

For each individual's last prescription during the study period (n=149,621), the duration that the prescription lasted for could not be calculated (for 29.3% of individuals, this was their only prescription in the study period). For the remaining prescriptions, the median time until a repeat was filled was 48 days (interquartiles 27 and 93 days), with a range of 1 to 2981 days.

The median estimated inhaled salbutamol amount was 124.2mcg per day, with interquartiles of 45.2 and 360.4mcg. The range of observed daily estimates was 4.1 to 200,000mcg, with the latter being roughly equivalent to 8 full inhalers being consumed on a single day (and thus clearly erroneous). Outlier values were observed when high amounts were obtained and then a subsequent refill was made shortly after. For example, there were 7618 (0.4%) cases in which the estimated daily use was equal to the amount dispensed, as another prescription was obtained the very next day.

The InterQuartile Range (IQR) for the estimated inhaled salbutamol amount was 315.2mcg. There was less variation within each individual's estimates, with a median within-person IQR of 82.0. The variation within a person was roughly equal to the variation within a person-year, however, with a median within-person-year IQR of 93.7. The Spearman correlation for an individual's median estimate from one year to the next was 0.67.

The median daily inhaled salbutamol amount increased across age categories: 77.5mcg in the under 18s, 88.9mcg in the 18-35s, 136.4mcg in the 36-55s, 180.2mcg in the 56-75s, and 202.0mcg in the those aged over 75 (Wilcoxon Rank Sum test $p<0.001$ for each age group increment's pairwise difference). The median amount also increased consistently from highest SIMD quintile (least deprived) to lowest, at 97.3mcg, 106.4mcg, 121.6mcg, 141.8mcg, and 159.4mcg, respectively ($p<0.001$ for each quintile increment's pairwise difference). Finally, the median daily amount was higher for men (135.1mcg) than women (115.6mcg, $p<0.001$). This finding was consistent across age groups, as shown in Figure 1.

Table 3: Median and Interquartile Range of Daily Inhaled Salbutamol (micrograms) by demography.

Factor	Level	Median	IQR
Sex	Male	135.14	48.54 - 387.10
	Female	115.61	42.64 – 387.10
Age Group	Under 18	77.52	33.78 – 190.00
	18-35	88.89	34.42 – 277.78
	36-55	136.36	47.17 – 394.74
	56-75	180.18	60.42 – 476.19
	Over 75	202.02	73.26 – 487.80
Scottish Index of Multiple Deprivation	1 (Most deprived)	159.36	52.22 – 444.44
	2	141.84	48.43 – 408.16
	3	121.58	45.05 – 357.14
	4	106.38	41.11 – 312.50
	5 (Least deprived)	97.32	39.45 – 270.27

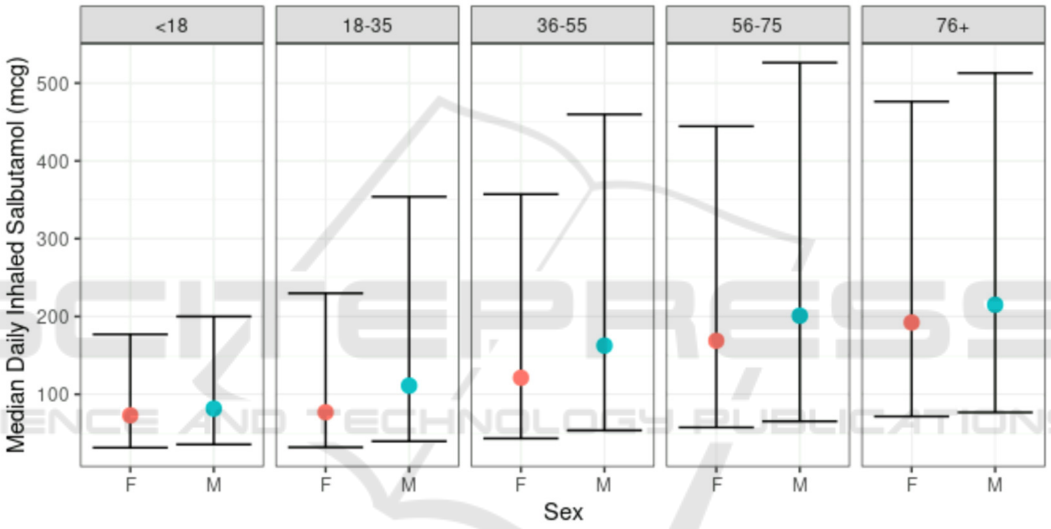

Figure 1: Boxplot of the Daily Inhaled Salbutamol (micrograms), stratified by Age Group and Sex. The central dot denotes the median value, and the error bars denote the interquartile range.

3.3 Non-inhaled Salbutamol Use

5799 people had at least one prescription for non-inhaled salbutamol (tablets, injections, or nebulising solution) during the study period, of whom 5058 also had inhaled salbutamol (87.2%). Conversely, only 3.4% of individuals with prescriptions for inhaled salbutamol also had non-inhaled salbutamol prescriptions. Those with at least one prescription for non-inhaled salbutamol had a median of three such prescribing events, with interquartiles 1 to 13 (range 1 to 254).

The median daily inhaled salbutamol amount was lower (120.5mcg, interquartiles 44.3 to 354.0mcg) in person-years without non-inhaled salbutamol prescribed, compared to years in which at least one prescription for non-inhaled salbutamol was filled (496.9mcg, interquartiles 200.0 to 975.6mcg, Wilcoxon Rank Sum test $p<0.001$). Indeed, it was also higher in those with any non-inhaled salbutamol prescribed during the study period (384.6mcg, interquartiles 143.4 to 800.0mcg) compared to those with none (117.0mcg, interquartiles 43.3 to 344.8mcg, $p<0.001$).

4 DISCUSSION

4.1 Principal Findings

5% of prescriptions were identified as salbutamol-based asthma symptom reliever medications, of which 97% were inhaled formulations. In years containing at least one inhaled SABA prescription, a

median of 3 cannisters were obtained. Using the GINA threshold of 600-doses (Reddel et al., 2021), a median of 66.7% of each individual's person-years could be classed as periods of over-use (range 11.1% - 100%, interquartiles 37.5% - 88.9%). The median time until a repeat was filled, for people with more than one SABA prescription, was 48 days.

The median estimated daily inhaled salbutamol amount was 124.2mcg (interquartiles 45.2 and 360.4mcg). The median of the interquartile range for daily estimates within a person-year was 82.0mcg, and there was moderate-strong correlation between the median from one person-year to the next (Spearman correlation coefficient = 0.67).

In a series of pairwise Wilcoxon Rank Sum tests, higher median daily inhaled salbutamol was found to be significantly associated with being older, male, or living in an area of higher deprivation. The median daily inhaled salbutamol amount was higher in the 3.4% of individuals with any non-inhaled salbutamol prescribed during the study period. For these individuals, the median daily inhaled salbutamol was higher in years in which non-inhaled salbutamol was also prescribed.

4.2 Results in Context

Many previous studies in the literature estimated daily inhaled SABA use over the duration of a year (Blakey et al., 2017; Disantostefano et al., 2016; FitzGerald et al., 2017; Lugogo et al., 2021; Makhinova et al., 2015; Stanford et al., 2012). In this study, we found that substantial variation within a year was commonplace, with a median within-person-year interquartile range of 89.3mcg. Studies such as Stanford *et al.* (2012), Blakey *et al.* (2017) , and Fitzgerald *et al.* (2017) have successfully demonstrated that SABA use in the previous year is a predictive factor for incidence of asthma attacks. Assuming that SABA over-reliance is a contributory factor to this increased risk, rather than simply acting as a marker for increased asthma symptoms or reduced symptom control, the ability to detect short-term changes in SABA use may facilitate more timely detection of increased risk in order to aid intervention.

Another common way of utilising asthma symptom reliever inhalers for assessing symptom control is to calculate the ratio of symptom controller to reliever medication prescriptions. This may be either as the number of prescriptions or cannisters themselves (Baltrus et al., 2017; Lieu, Capra, Quesenberry, Mendoza, & Mazar, 1999) or the ratio of inhaled corticosteroid (typically converted to budesonide equivalent as some medications such as Ciclesonide are double potency) to salbutamol in micrograms (Gonem, Cumella, & Richardson, 2019).

Finally, this study only used inhaled salbutamol for the primary analyses, with prescriptions of other formulations (including solutions for nebuliser devices) evaluated as a potential risk modifier. Other formulations may be prescribed for very young children or those for whom inhaled therapy cannot be used reliably, or in the case of acute exacerbation (Pharmaceutical Press Joint Formulary Committee, 2019b). Other studies, such as Stanford *et al.* converted nebulised doses to the equivalent inhaled doses (Stanford et al., 2012), however the use of non-inhaled formulations has been identified previously as a strong risk predictor for adverse outcomes. For example, Paris et al. found a 21.6 times increase in hazard ratio for asthma-related hospitalisation for every daily nebulised salbutamol use (Paris et al., 2008).

One limitation of the assessment of inhaled salbutamol use from prescription records is that prescription refills do not perfectly correspond to medication usage. This is a limitation of this type of analysis for any type of medication, however for reliever medications it may be more common. For example, individuals may wish to have multiple inhalers at different locations, and may also be more likely to misplace inhalers due to their irregular use. Estimating daily inhaled SABA use over multiple refills may mitigate this affect somewhat, as periods of overlap of inhalers may be evened out.

5 CONCLUSIONS

In this study, we have estimated the median inhaled SABA dose per day and the proportion of individuals with GINA-defined SABA over-use from our Scottish cohort, and identified factors associated with higher inhaled SABA use: increased age, male sex, higher deprivation, and history of non-inhaled SABA prescription.

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