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ORIGINAL RESEARCH

Characterisation of the Australian Adult Population Living with Asthma: Severe - Exacerbation Frequency, Long-Term OCS Use and Adverse Effects

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On behalf of the OPCA Improving Asthma outcomes in Australia Research Group

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Introduction: Asthma poses a significant burden for the Australian population. Understanding severe exacerbation rates, and steroid-related burden for adults diagnosed with asthma stands to offer insights into how this could be reduced.

Methods: Electronic medical records (EMR) and questionnaires from the Optimum Patient Care Research Database Australia (OPCRDA) were utilised retrospectively. OPCRDA is a real-world database with >800,000 medical records from Australian primary care practices. Outcomes were severe asthma exacerbations in Australian adults, over a 12-month period, stratified by Global Initiative for Asthma (GINA) treatment intensity steps, and steroid associated comorbidities.

Results: Of the 7868 adults treated for asthma, 19% experienced at least one severe exacerbation in the last 12-months. Severe exacerbation frequency increased with treatment intensity (≥1 severe exacerbation GINA 1 13%; GINA 4 23%; GINA 5a 33% and GINA 5b 28%). Questionnaire participants reported higher rates of severe exacerbations than suggested from their EMR (32% vs 23%) especially in steps 1, 4 and 5. Patients repeatedly exposed to steroids had an increased risk of osteoporosis (OR 1.95, 95% CI 1.43–2.66) and sleep apnoea (OR 1.78, 95% CI 1.30–2.46).

Conclusion: The Australian population living with GINA 1, 4, 5a and 5b asthma have high severe exacerbation rates and steroid-related burden, especially when compared to other first world countries, with these patients needing alternative strategies or possibly specialist assessment to better manage their condition.

Keywords: asthma, exacerbations, oral corticosteroids, adults, Australia

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Introduction

Asthma is a chronic respiratory condition characterised by underlying airway inflammation and bronchoconstriction, which can fluctuate in severity and frequency over time.[1] The prevalence of asthma in the Australian population is 11%, which is well above the 4% prevalence globally.[2,3] Thus, defining the level of control in terms of severe exacerbations and steroid burden can assist in reducing the burden of this disease.

Nationally, asthma accounts for over 70,000 emergency department presentations annually and is estimated to have a financial burden of A$770 million on the health-care system.[2,4] At an individual level, 24% of Australian patients with asthma reported missing work or school as a result of their condition, with a mean of 9.5 sick days annually and a 30% reduction in productivity when symptoms were at their worst.[5] Furthermore, a recent Australasian study found in a 12-month period, patients with severe asthma (confirmed by variable airflow limitation within the last 10 years and poor control despite high dose inhaled corticosteroids and a second controller), had a median of 2 oral corticosteroid (OCS) bursts for treatment of exacerbations, 24% of them required emergency medical care, and 22% were hospitalised due to their condition.[6] Asthma also results in approximately 400 potentially preventable deaths in Australia per year, a mortality rate that has changed very little over the past decade despite advances in management practices.[7]

OCS is effective for the treatment of exacerbations, however repetitive bursts or long-term administration can cause adverse effects.[8,9] There is a clear dose-response relationship between OCS use and increased risk of osteoporosis, osteoporotic fractures, weight gain/obesity, type 2 diabetes mellitus, hypertension, peptic ulcers, cataracts, sleep apnoea, anxiety and depression.[9,10] Thus, characterising the demographic features of this population in relation to asthma treatment intensity, defined as Global Initiative for Asthma (GINA) treatment intensity steps, OCS use and their relationship to comorbid conditions, stands to offer potential benefits especially where alternative treatment or management strategies exist.

GINA treatment intensity steps are internationally recognised, population-level preferred and alternative pharmacological recommendations for the management of asthma.[11] The principles underpinning the asthma cycle of care are mirrored in the treatment intensity steps, in that a patient is not permanently assigned to any one category; rather they can be stepped up or down in treatment intensity depending on their needs at any point. Thus, when examining severe exacerbations in the Australian adult population living with asthma, GINA treatment intensity steps allow for stratification of patients based on their current medications and comparison to international populations due to its acceptance globally. Notably, there are five steps in the GINA stratification system,[11] however for the purposes of the current study, we have subdivided step 5 into 2 sub-steps. Step 5a; refers to patients prescribed high dose inhaled corticosteroids, and Step 5b refers to patients receiving biologics or long-term OCS therapy (Figure 1). This segregation allowed for a more detailed understanding of ICS and OCS use in Australian adults living with asthma. Additionally, in the current study, step 1 has been restricted to patients solely using SABA to manage their condition, as opposed to as needed ICS/LABA.

International populations with asthma have been previously described via the European and Asian REALISE surveys,[12,13] and Reddel et al[14] has characterised the Australian population living with asthma. A notable limitation of these studies was that data collection utilised web-based surveys, increasing the possibility of responder bias, no matter how methodical the approach. The use of electronic medical records (EMR) as a source of data could help to overcome this by including all patients who have received an episode of asthma-related care, irrespective of the severity of their condition. Bloom et al[15] have recently published an EMR-based description of asthma in the UK utilising linked primary and secondary care data and categorised patients by age range. The ability to use data extracted from EMR and supplement this with patient reported information on factors such as smoking status, self-managed exacerbations, medication use, level of control and comorbidities could offer insights into patient behaviours and the associated impact of this disease. Characterisation of patients based on age is also important as the high prevalence of asthma in the community indicates that many older people suffer from asthma and suffer disproportionally in terms of morbidity, comorbidity and mortality.[16,17]

The primary aim of the present study was to describe the characteristics of the Australian adult population living with asthma, in younger (18–54 years) and older (≥55 years) adults with a focus on severe exacerbations (over a 12-month period), as per GINA treatment intensity steps and comorbidity frequency. The secondary aim was to explore repeated

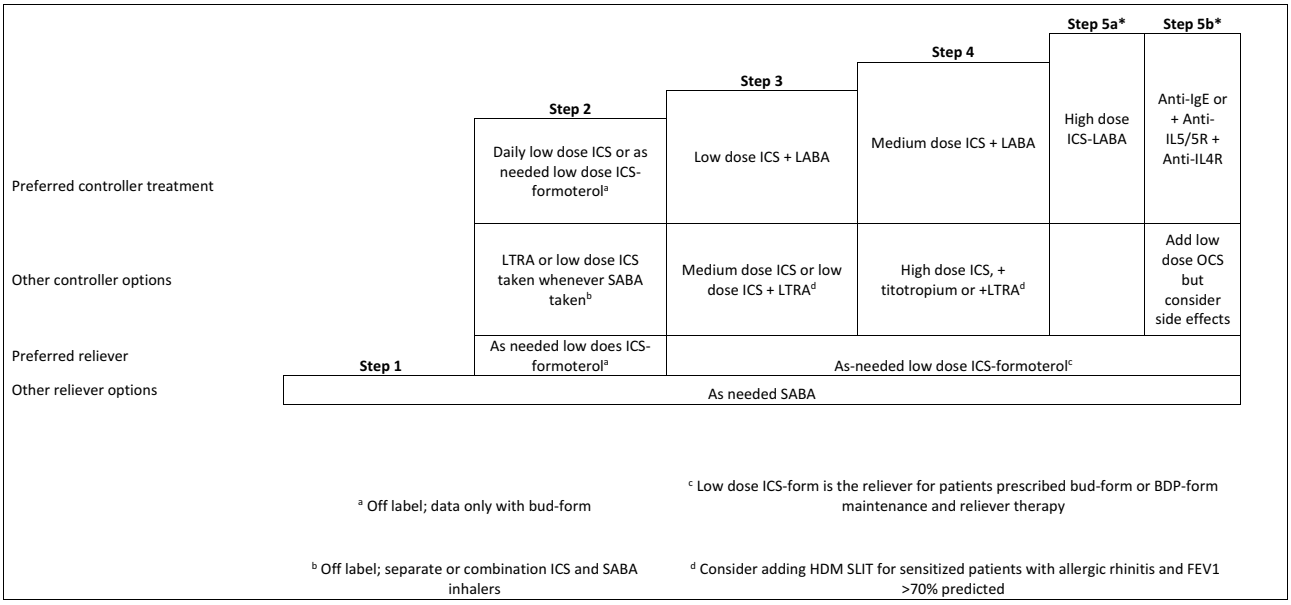

Figure 1 GINA treatment intensity steps for adults living with asthma. Adapted from Global Initiative for Asthma, 2020; *Step 5 is not traditionally subdivided into two groups 5a and 5b, this has been done for the purposes of the present investigation to allow for a more detailed understanding of ICS and OCS use in Australian adults living with asthma.

Abbreviations: BDP-form, beclometasone-formoterol; Bud-form, budesonide formoterol; FEV1, forced expiratory volume in 1 second; HDM SLIT, house dust mite subcutaneous allergy immunotherapy; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL4R, interleukin 4 receptor; IL5/5R, interleukin 5/5 receptor; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short acting beta agonist.

steroid exposure with associated comorbid conditions, with the purpose of better understanding steroid burden in the Australian population.

Materials and Methods

Study Design

This study is a historical, observational study using data derived from the Optimum Patient Care Research Database Australia (OPCRDA) (https://optimumpatientcare.org.au/opcrda/). OPCRDA is a real world, longitudinal, research database of anonymised primary care EMR and matched patient questionnaires completed as part of practice audits and quality improvement. Patients were given the option to complete questionnaires which captured information on body mass index (BMI), smoking status, the presence of allergic rhinitis, asthma control, severe exacerbations, management plans, and classification and quantification of medications used (Appendix 1 contains a full list of questionnaire questions). Quantification of actual prescriptions dispensed is not captured by Australian primary care EMR, rather prescriptions issued (which can permit multiple dispensations for a fixed period) are recorded, highlighting the value of supplementing this data with patient completed questionnaires. Declining to complete the questionnaire did not exclude a patient's EMR data from being captured and used in the present investigation. Patient data used in the present study was collected from 21 individual primary care practices, spread across 5 Australian states or territories, Queensland (8), New South Wales (9), Australian Capital Territory (1), Victoria (1) and South Australia (2).

Inclusion Criteria and Data Extraction

Criteria for EMR inclusion was age ≥18 years and a clinician diagnosis of active asthma. Active asthma was defined as the presence of a diagnostic asthma code within the EMR and a prescription for at least one asthma medication outlined by the National Asthma Council,[18] within the last two years. Exclusion criteria were a diagnosis of chronic obstructive pulmonary disease (COPD), cystic fibrosis or any other chronic respiratory condition. Data were extracted from the EMR using Best Practice (https://bpsoftware.net/) and Medical Director (https://www.medicaldirector.com/) disease codes and coded data derived from free text clinical notes. The reference date for inclusion of EMR data was 30th of April 2021.

Study Population and the Questionnaire Sub-Population

Use of mixed data acquisition methods, EMRs and patient-completed questionnaires, uniquely positions this study to compare the demographics and clinical features of the total study population and questionnaire sub-population. Data presented for the total study population includes patients who did and did not complete the questionnaire and is derived exclusively from EMRs. Data for the questionnaire sub-population were derived from EMRs and patient-completed questionnaires. Notably, the questionnaires were used to examine differences between EMR and self-reported rates of severe exacerbations, patterns of medication prescription versus usage and symptom control.

Outcomes and Variables

The definition of severe exacerbations and ICS-related terms have been defined in Table 1. The first primary outcome was severe asthma exacerbations over a 12-month period, by GINA 2020 treatment algorithm: intensity steps[11] and comorbidity frequency (Table 1). A patient's GINA treatment intensity step was determined by the medications used at the time of data extraction, an approach that is consistent with previously published studies.[15,19] However, unlike prior studies, GINA step 5 was split into two subgroups, 5a, patients prescribed high dose inhaled corticosteroids, and 5b, patients receiving biologics or long-term OCS therapy (Figure 1; Table 1). Other key outcomes included the level of asthma symptom control as per GINA treatment intensity steps, OCS prescription patterns and prevalence of co-morbidities. GINA 2020[11] symptom control questions were included in the questionnaires and used to stratify the level of symptoms control. OCS prescription patterns included the number of scripts administered with and without repeat authorisations for both acute and long-term regimes. Comorbidities of interest were those potentially related to steroid use,[9] type-2 asthma[20] (Appendix 2 contains a full list of disease codes and free text terms used to define allergies and allergic asthma) or confounders for asthma, including obesity (Table 1; Appendix 3 contains a full list of disease codes and free text terms used to define obesity). The secondary outcome was the association of steroid-related comorbidities following repeated exposure to OCS as previously published (Table 1).[9]

Statistical Analysis

Statistical analysis was performed using R for Windows version 4.0.2. Demographic data were summarised as frequencies and percentages, separately for the total study cohort and questionnaire sub-population, by age-group. Statistics were conducted for OCS use and related comorbidities using Pearson's chi-squared test statistic to compare the groups and logistic regressions to estimate the OR and the 95% CIs, adjusting, when indicated, for potential confounding variables such as age and gender.

Data for the primary outcome are presented for the total study cohort (as recorded in EMRs) and questionnaire sub-population (recorded as both the EMR data and self-reported questionnaire responses). These populations have further been categorised based upon age; 18–54 years and >55 years, consistent with demographic analysis of other adult populations living with asthma.[15] Self-reported severe exacerbation rates in questionnaire participants were cross matched with their EMR.

Table 1 Definition of Severe Exacerbation and ICS-Related Terms Used in the Present Study

	Definition
Severe exacerbation	Needing a course of acute OCS (defined as ≥ 20mg per day), the need to seek emergency medical services, or a hospital admission.
High dose inhaled corticosteroids	Total daily dose of extrafine beclometasone >400 mcg, budesonide >800 mcg, ciclesonide >320 mcg, fluticasone furoate ≥200 mcg, fluticasone propionate >500 mcg.[33]
Obesity	BMI >30 and an associated disease code or coded data within the patient's EMR.
Repeated steroid exposure	More than four exacerbations requiring acute OCS or the requirement of long-term OCS.

Abbreviations: BMI, body mass index; EMR, electronic medical record; mcg, micrograms; mg, milligrams; OCS, oral corticosteroids.

Results

Patients

Based upon prescriptions or diagnostic codes in EMR, 51,307 adults were identified as potentially having asthma or COPD, representing 6.4% of patients in the database. Of these, 27,230 (53%) had no formal diagnosis recorded; however, 7868 were identified as having active asthma and were included in the current study (Figure 2). Twenty-one primary care practices (20 in major cities, 1 in regional Australia as defined by the 2016 Remoteness area categories[21]) participated in this study.

Characterisation of the Australian Adult Asthmatic Population

Sixty-one percent of the total study cohort were aged between 18 and 54 years, 64% were female, 67% recorded a smoking status as never smoked and 47% were obese (Table 2). Over half of the total study cohort also had moderate to high asthma treatment intensity, correlating to GINA step 3 (18%), 4 (27%), 5a (14%), and 5b (2%) (Table 2). Age was associated with greater treatment intensity and reliance on biologics or long-term OCS therapy (GINA step 5a 18–54 years 12%, >55 years 16%; GINA step 5b 18–54 years 1%, >55 years 3%) (Table 2).

Total Study Population Vs Questionnaire Sub-Population

A subgroup of 515 individuals had accompanying questionnaire data, representing 6.5% of the total cohort (Table 2). Differences in GINA treatment intensities and use of biologics or long-term OCS were observed between the total study population (GINA 1 33%; GINA 5b 2%) and the questionnaire subgroup (GINA 1 21%; GINA 5b 12%) (Table 2). Variations in OCS prescription patterns were also observed between the total study population (acute OCS 19%; acute OCS with repeats 3%) and the questionnaire subgroup (acute OCS 23%; acute OCS with repeats 8%) (Table 2).

Co-Morbidities

Concurrent comorbidities were common in both groups, with 61% of the total cohort and 83% of the questionnaire subgroup having three or more comorbidities, with age related to frequency (Table 2). Based on EMR data, allergies/allergic asthma (73%), obesity (49%) and sleep apnoea (43%) were common comorbidities. Whilst self-reported allergic rhinitis (87%) was the most common comorbidity for questionnaire participants.

Severe Exacerbations

Frequency of severe exacerbations stratified per GINA treatment intensity step is presented in Figures 3A–C. Figure 3A and B presents frequency of severe exacerbations as outlined in EMR for the total study population, and questionnaire participants, respectively. Whilst Figure 3C presents frequency of self-reported severe exacerbations for the questionnaire participants. Nineteen percent of the total study population and 23% of the questionnaire participants experienced one or more severe exacerbations during the 12-month study period, as documented in their EMR (Figure 3A and B). Thirty-two percent of questionnaire respondents self-reported experiencing one or more severe exacerbations (Figure 3C).

Severe Exacerbations Frequency by GINA Treatment Intensity

Increased GINA treatment intensity step was associated with increased frequency of severe exacerbations for both the total study population and the questionnaire participants (Figure 3A–C). As outlined in EMRs, 5% of the total study cohort experienced 2 or more severe exacerbations in the 12-month study period (Figure 3A). When stratified per GINA step, 2% of GINA 1, 3% of GINA 2, 3% of GINA 3, 5% of GINA 4, 11% of GINA 5a and 10% of GINA 5b patients experienced 2 or more severe exacerbations (Figure 3A). A similar pattern was also observed in the questionnaire sub-population (Figure 3B). An increase in severe exacerbation frequency with increased GINA step was even more apparent in self-reports by the questionnaire population (Figure 3C). Whereby 15% of the questionnaire population self-reported 2 or more severe exacerbations in the 12-month study period (Figure 3C). When stratified for GINA step, 12% of GINA 1, 6% of GINA 2, 10% of GINA 3, 12% of GINA 4, 32% of GINA 5a and 16% of GINA 5b patients self-reported two or more severe exacerbations (Figure 3C).

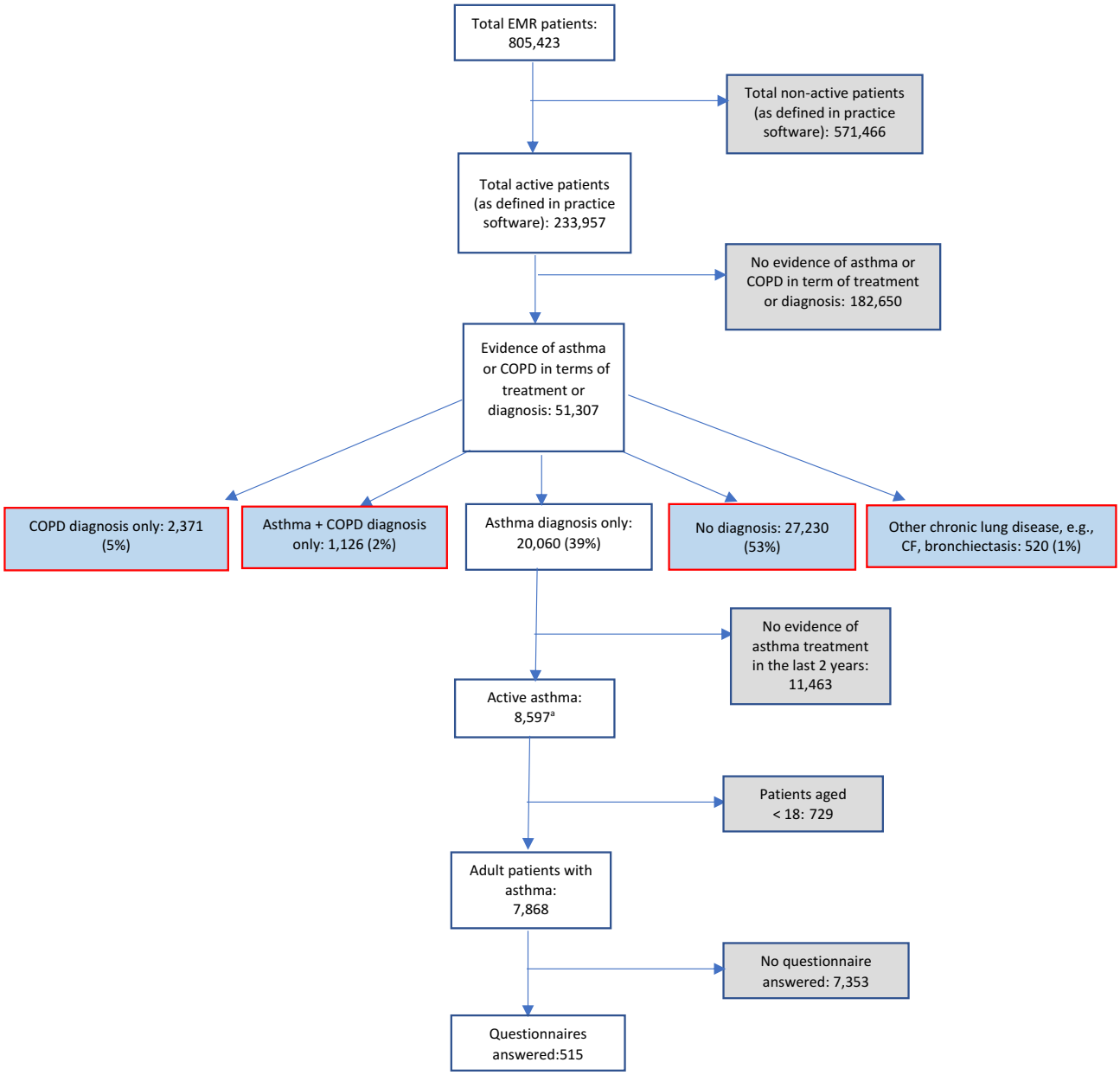

Figure 2 Patient flow showing eligibility criteria for inclusion. [a]Active asthma patients are defined as those who received asthma therapy in the last 2 years.
Abbreviations: CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; EMR, electronic medical records.

Cross Matching EMR Recorded and Self-Reported Severe Exacerbations in Questionnaire Participants

Cross-matching EMR recorded and self-reported severe exacerbations by questionnaire participants shows severe exacerbation frequency is under-reported in EMRs (Figure 4). For example, 75 patients self-reported ≥1 severe exacerbation, however the same patients had zero severe exacerbations recorded in their EMR (Figure 4).

Asthma Control

Asthma control status was assessed using self-reported questionnaire responses (Figure 4). Sixty-one percent of questionnaire respondents have either uncontrolled or partially controlled asthma. Higher GINA treatment intensity

Table 2 Demographics of the Australian Adult Population Living with Asthma, as a Whole and by Age Rage. Data Was Extracted from Electronic Medical Records and Self-Reported by Questionnaire Participants

Population	EMR Data for Total Study Cohort			Self-Reported Responses Supplemented with EMR Data for Questionnaire Participants[a]		
	18–54 Years Old	>55 Years Old	Total Study Cohort	18–54 Years Old	>55 Years Old	All Questionnaire Participants
Demographic characteristic						
	N = 4778	N = 3090	N = 7868	N = 226	N = 289	N = 515
Gender, n (%)						
Non-missing	4758	3086	7844	226	289	515
Female	2894 (61%)	2117 (69%)	5011 (64%)	164 (73%)	198 (69%)	362 (70%)
Smoking status, n (%)						
Non-missing	4209	2899	7108	225	315	514
Never	2854 (68%)	1923 (66%)	4777 (67%)	151 (67%)	178 (62%)	329 (64%)
Current	705 (17%)	168 (6%)	873 (12%)	16 (7%)	18 (6%)	34 (7%)
Former	650 (15%)	808 (28%)	1458 (21%)	58 (26%)	93 (32%)	151 (29%)
BMI, n (%)						
Non-missing	2501	2459	4960	182	258	440
Underweight (<18.5)	49 (2%)	19 (1%)	68 (1%)	3 (2%)	1 (0%)	4 (1%)
Normal (>18.5 - <25)	659 (26%)	387 (16%)	1046 (21%)	56 (31%)	47 (18%)	103 (23%)
Overweight (>25 - <30)	716 (29%)	801 (33%)	1517 (31%)	49 (27%)	79 (31%)	128 (29%)
Obese (>30)	1077 (43%)	1252 (51%)	2329 (47%)	74 (41%)	131 (51%)	205 (47%)
GINA step, n (%)						
Step 1 (as needed SABA)	1726 (36%)	852 (28%)	2578 (33%)	64 (28%)	46 (16%)	110 (21%)
Step 2 (ICS only low dose)	239 (5%)	124 (4%)	363 (5%)	14 (6%)	18 (6%)	32 (6%)
Step 3 (ICS only medium dose or ICS/LABA low dose)	1001 (21%)	644 (21%)	1645 (18%)	48 (21%)	60 (21%)	108 (21%)
Step 4 (ICS only high dose or ICS/LABA medium dose)	1207 (25%)	882 (29%)	2089 (27%)	48 (21%)	78 (27%)	126 (24%)
Step 5a (ICS ICS/LABA high dose)	578 (12%)	488 (16%)	1066 (14%)	36 (16%)	42 (15%)	78 (15%)
Step 5b (long-term OCS or biologics)	27 (1%)	100 (3%)	127 (2%)	16 (7%)	45 (16%)	61 (12%)
OCS prescription patterns						
Prescription of acute OCS	891 (19%)	630 (20%)	1521 (19%)	43 (19%)	75 (26%)	118 (23%)
Prescription of acute OCS with repeats	135 (3%)	125 (4%)	260 (3%)	13 (6%)	27 (9%)	40 (8%)
Prescription of long-term OCS	81 (2%)	187 (6%)	268 (3%)	10 (4%)	16 (6%)	26 (5%)

(*Continued*)

Table 2 (Continued).

Population	EMR Data for Total Study Cohort			Self-Reported Responses Supplemented with EMR Data for Questionnaire Participants[a]		
	18–54 Years Old	>55 Years Old	Total Study Cohort	18–54 Years Old	>55 Years Old	All Questionnaire Participants
Prescription of long-term OCS with repeats	37 (1%)	115 (4%)	152 (2%)	3 (1%)	7 (2%)	10 (2%)
N of comorbidities, n (%)						
0	468 (10%)	101 (3%)	569 (7%)	5 (2%)	0 (0%)	5 (1%)
1	908 (19%)	226 (7%)	1134 (14%)	13 (6%)	6 (2%)	19 (4%)
2	943 (20%)	393 (13%)	1336 (17%)	40 (18%)	23 (8%)	63 (12%)
3 or more	2459 (51%)	2370 (77%)	4829 (61%)	168 (74%)	260 (90%)	428 (83%)
Comorbidities, n (%)						
Potentially steroid related comorbidities						
Diabetes	272 (6%)	584 (19%)	856 (11%)	18 (8%)	49 (17%)	67 (13%)
Osteoporosis	907 (19%)	1094 (35%)	2001 (25%)	60 (27%)	127 (44%)	187 (36%)
Obesity	2316 (48%)	1548 (50%)	3864 (49%)	116 (51%)	164 (57%)	280 (54%)
Hypertension	284 (6%)	1160 (38%)	1444 (18%)	15 (7%)	110 (38%)	125 (24%)
Sleep apnoea	1699 (36%)	1672 (54%)	3371 (43%)	100 (44%)	181 (63%)	281 (55%)
Heart disease[b]	41 (1%)	221 (7%)	262 (3%)	6 (3%)	28 (10%)	34 (7%)
Depression/anxiety	1761 (37%)	1130 (37%)	2891 (37%)	107 (47%)	104 (36%)	211 (41%)
Type-2 asthma comorbidities						
Allergies or allergic asthma[c]	3141 (66%)	2586 (84%)	5727 (73%)	181 (80%)	263 (91%)	444 (86%)
Atopic dermatitis	1244 (26%)	1002 (32%)	2246 (29%)	73 (32%)	83 (29%)	156 (30%)
Allergic rhinitis	1001 (21%)	824 (27%)	1825 (23%)	195 (86%)	252 (87%)	447 (87%)
Nasal polyps	14 (0%)	32 (1%)	46 (1%)	2 (1%)	7 (2%)	9 (2%)
Confounding asthma comorbidities						
GERD	648 (14%)	1156 (37%)	1804 (23%)	45 (20%)	107 (37%)	152 (30%)

Notes: [a]Questionnaires captured data on age, gender, smoking status, BMI, GINA step, requirement for long-term OCS, number of comorbidities, and occurrence of allergic rhinitis; the occurrence of other comorbidities other than allergic rhinitis was provided by EMR for questionnaire participants. [b]Defined as ischemic, arrhythmia, conductive, valvular, myopathic pathologies, see Appendix 3 for a full list of diagnostics read codes and free text search terms; [c]See Appendix 4 for a full list of diagnostics read codes and free text search terms.

Abbreviations: BMI, body mass index; EMR, electronic medical records; GERD, gastroesophageal reflux disease; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; ICS/LABA, inhaled corticosteroids/long-acting beta agonists; OCS, oral corticosteroids; SABA/ICS, short acting beta agonists/inhaled corticosteroids.

steps were associated with an increased likelihood of having uncontrolled asthma (Figure 4). For example, 18% of GINA 1, 22% of GINA 2, 26% of GINA 3, 25% of GINA 4, 37% of GINA 5a and 38% of GINA 5b patients self-reported experiencing uncontrolled asthma (Figure 4).

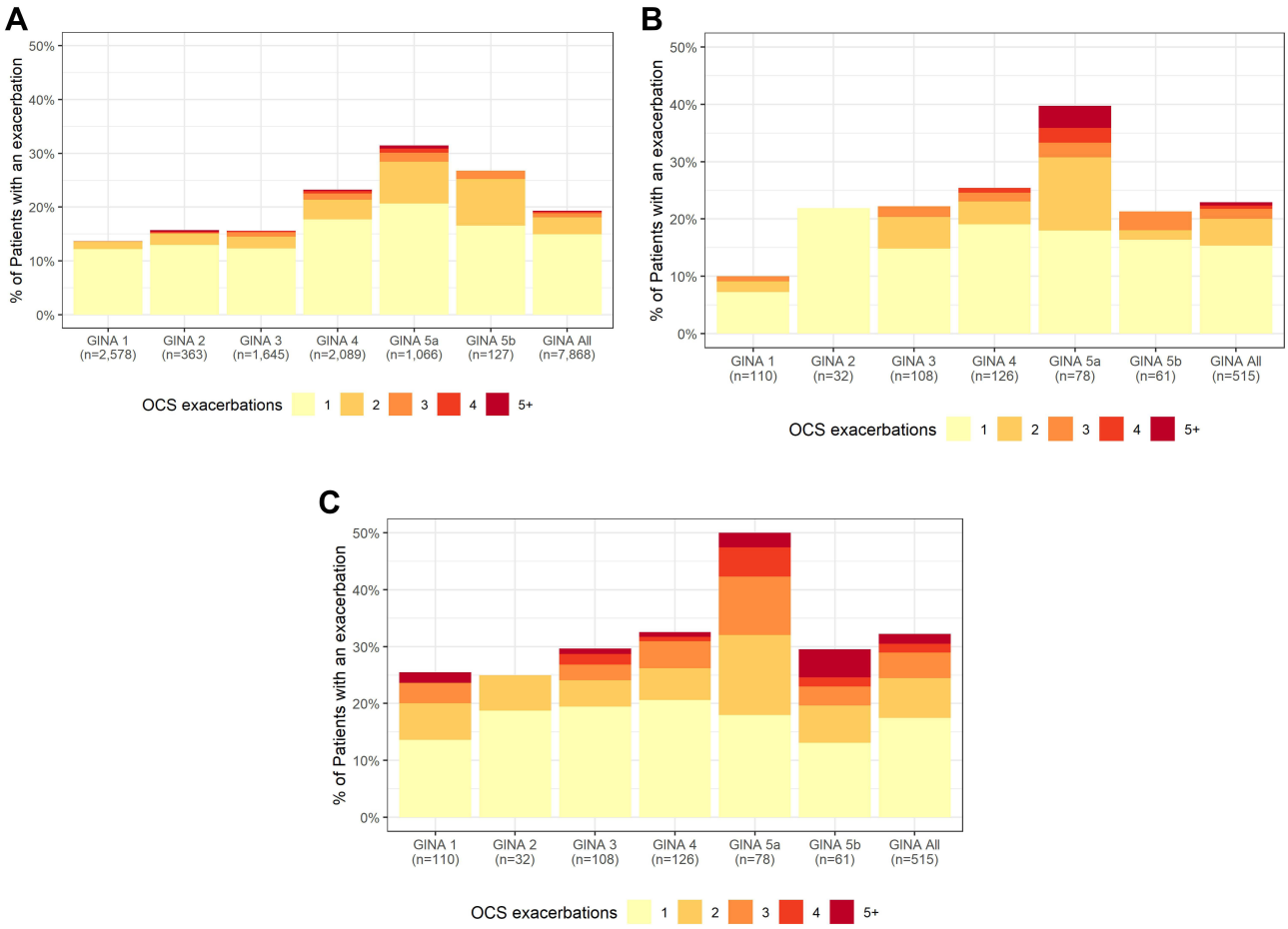

Figure 3 (**A**) Exacerbation frequency as per GINA treatment intensity for the total study population as per electronic medical records. (**B**) Exacerbation frequency as per GINA treatment intensity for the questionnaire respondents as per electronic medical records. (**C**) Exacerbation frequency as per GINA treatment intensity as self-reported by questionnaire respondents. GINA 1 is defined as, as needed short acting beta agonists; GINA 2 is defined as only low dose inhaled corticosteroids (ICS); GINA 3 is defined as ICS only at a moderate dose or ICS/long-acting beta agonist (LABA) combination at a low dose; GINA 4 is defined as ICS at a high dose or ICS/LABA at a moderate dose; GINA 5a is defined as ICS at a high dose; 5b is defined as biologics or chronic oral corticosteroid therapy.
Abbreviations: GINA, Global Initiative for Asthma; EMR, electronic medical records; OCS, oral corticosteroids.

Long-Term OCS Use and Related Co-Morbidities

The association between repeated high-intensity steroid exposure, defined as long term OCS use or experiencing four or more severe exacerbations requiring OCS bursts, and the development of comorbid conditions is shown in Table 3. When adjusted for age and gender, patients in the total study cohort who were repeatedly exposed to steroids had an increased risk of sleep apnoea (OR 1.78, 95% CI 1.30–2.46) and osteoporosis (OR 1.95, 95% CI 1.43–2.66) (Table 3). Unadjusted odds ratios also indicate that patients who had repeated high-intensity steroid exposure had an increased risk of sleep apnoea (OR 2.29, 95% CI 1.68–3.15) and osteoporosis (OR 2.55, 95% CI 1.88–3.46), as well as diabetes (OR 2.14, 95% CI 1.44–3.09), hypertension (OR 2.51, 95% CI 1.82–3.43), and heart disease (OR 3.11, 95% CI 1.76–5.12) (Table 3).

Discussion

This study describes a large, representative cohort of adults in Australia living with asthma, managed within primary care. Almost one-fifth of the cohort experienced at least one severe exacerbation requiring acute OCS therapy, and just under a quarter of these individuals had multiple episodes. Severe exacerbation rates were slightly higher in EMRs of questionnaire respondents. Self-reported rates of severe exacerbations were higher again in questionnaire respondents, with over half of the patients categorised as GINA step 5a or 5b who experienced a severe exacerbation reporting

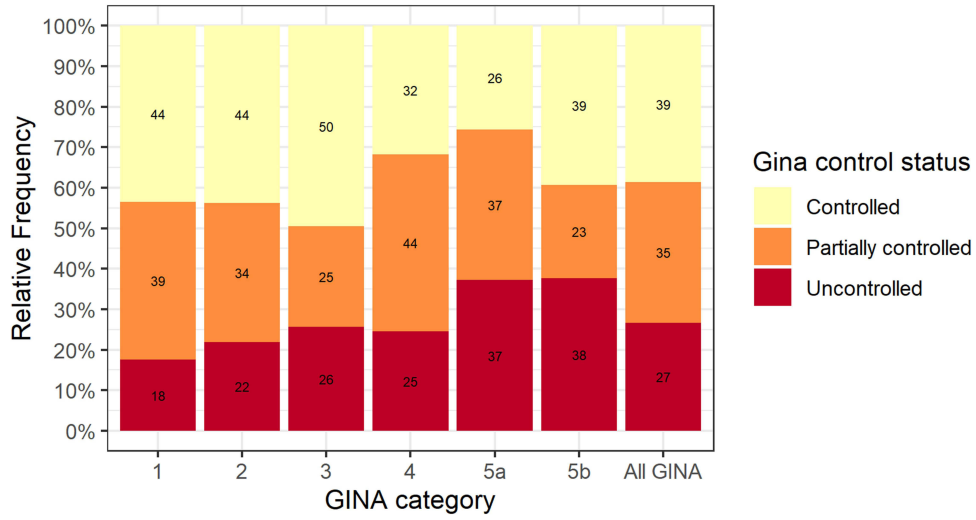

Figure 4 Frequency of asthma control stages by treatment intensity for questionnaire participants as defined by Global Initiative for Asthma control status questions. GINA 1 is defined as, as needed short acting beta agonists/inhaled corticosteroids (ICS); GINA 2 is defined as only low dose ICS; GINA 3 is defined as ICS only at a moderate dose or ICS/long-acting beta agonist (LABA) combination at a low dose; GINA 4 is defined as ICS at a high dose or ICS/LABA at a moderate dose; GINA 5a is defined as ICS at a high dose; 5b is defined as biologics or chronic oral corticosteroid therapy.
Abbreviation: GINA, Global Initiative for Asthma.

multiple episodes. GINA treatment intensity step was associated with the frequency with which severe exacerbations occurred and recurrent OCS use increased the risk of developing osteoporosis and sleep apnoea. Allergic rhinitis was the most common comorbidity; however, it was underreported in the EMR when compared to questionnaire data.

The incidence of severe asthma exacerbations in the present study (19% of the total study population and 23% of the questionnaire participants as per EMRs) is slightly higher than what has been reported in EMR-based studies from the UK (18%)[22,23] and USA (13%).[22] However, it is consistent with previously published rates of 29%[14] and 23%[24] in the Australian population, from survey-based studies. Additionally, the variation in severe exacerbation rates observed between the EMRs of questionnaire participants and their self-reported responses suggest the frequency is underreported in the former. Whilst it

Table 3 Odds Ratio and 95% Confidence Intervals for the Association Between Repeated High-Intensity Steroid Exposure (Defined as >4 Exacerbations or Requiring Long-Term Oral Corticosteroid Use) and the Development of Comorbid Conditions

Morbidity	EMR			
	>4 Exacerbations or Requiring Long-Term OCS	≤4 Exacerbations and Not Requiring Long-Term OCS	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Potential steroid related comorbidities				
Diabetes	35 (20%)	821 (11%)	2.14 (1.44–3.09)	1.36 (0.91–2.00)
Osteoporosis	79 (46%)	1922 (25%)	2.55 (1.88–3.46)	1.95 (1.43–2.66)
Obesity[b]	89 (52%)	3775 (49%)	1.11 (0.82–1.51)	1.11 (0.82–1.51)
Hypertension	61 (36%)	1383 (18%)	2.51 (1.82–3.43)	1.35 (0.94–1.92)
Sleep apnoea	108 (63%)	3263 (42%)	2.29 (1.68–3.15)	1.78 (1.30–2.46)
Heart disease	16 (9%)	246 (3%)	3.11 (1.76–5.12)	1.69 (0.94–2.87)
Depression/anxiety	72 (42%)	2819 (37%)	1.25 (0.91–1.69)	1.22 (0.89–1.66)

Notes: [a]Age and gender adjusted. [b]Defined from clinical notes or most recent BMI >30.
Abbreviations: CI, confidence interval; EMR, electronic medical records; OCS, oral cortico steroid OR, odds ratio.

would be advantageous to explore trends associated with underreporting of severe exacerbations (primary or secondary care), it was beyond the scope of the present investigation and future studies could consider this.

Similarly, the observation that 2% of the total study cohort were prescribed long-term OCS therapy is almost double what has been reported in the UK (1.3%).[25] Examining this by age range, Australian's aged >55 years were twice as likely to be prescribed long-term OCS to manage their condition in comparison to their UK counterparts.[15] Similarly, Australian's aged 18–54 years were three times as likely to be prescribed long-term OCS when compared to British adults of the same age.[15] This suggests Australians are heavily reliant on OCS to manage asthma especially when compared to other countries such as the UK. It is of note that over 50% of patients in the database who received asthma or COPD therapy had no formal diagnosis.

In relation to repeated use of OCS in managing asthma, either as maintenance therapy or frequent acute rescue courses, the current study supports existing literature which demonstrates an increased risk of adverse effects.[8,26,27] Whilst prior studies have shown a dose-response relationship between OCS use and a wide spectrum of adverse effects, the present study only observed an increased risk of developing osteoporosis and sleep apnoea, presumably due to the smaller study population in the present investigation when compared to others. Importantly, the continued demonstration that regular OCS use in asthma carries a treatment burden for patients encourages advocacy to adopt alternative or refined treatment strategies.

As for the underreporting of allergic rhinitis, this observation is consistent with previous studies showing at least 35.1% of Australian's purchasing over the counter medications for allergic rhinitis do not have a physician confirmed diagnosis.[28] Likewise, 90% of Australians diagnosed with asthma reported having rhinitis symptoms, however almost half were without a doctor's diagnosis.[29]

In the present investigation, supplementation of EMR with data derived from the questionnaires allowed for a more in-depth understanding of the Australian population living with asthma, thus limiting the reliance on one information source and in some cases enabling cross checking of results. The interpretation of both EMR and questionnaires, however, needs to be done with their respective limitations in mind.

The data management system used in Australian primary care is just starting to consolidate patient information and does not automatically track hospital presentations. As such, severe exacerbations associated with an emergency medical consultation in secondary care may be underreported in the current study. This idea is supported by variations in severe exacerbation rates self-reported by questionnaire participants and their EMR.

Similarly, surveys are subject to responder bias and can lead to mischaracterisation of the population, no matter how meticulous the methodology. To this point, only 6.5% of the total cohort completed the questionnaire. Additionally, participants aged >55 years were more likely to complete the questionnaire. This may explain why the use of biologics and long-term OCS as well as comorbidity frequency was higher in the questionnaire subgroup when compared to the total study population.

It is also concerning that there was a large variation in the use of long-term OCS between the total study cohort (2%) and questionnaire participants (12%). By definition, the use of long-term OCS to manage asthma symptoms is GINA 5b treatment intensity, and the high percentage of questionnaire participants self-reporting long-term OCS use raises questions of accuracy. It is possible that this variation has occurred due to differences in the data being reported. It is not clear why Australia has a higher burden of severe asthma exacerbations and overreliance on OCS. It is possible this may relate to differences in asthma severity between the Australian and international populations, short acting bronchodilators being available over the counter, and the Australian prescribing system allowing for the prescription of multiple courses of steroids to be issued without consultation in between. For example, in the current study approximately 1 in 5 patients prescribed OCS received this with authorisation for repeats (19%). However, the issuing of repeat authorisations may not solely reflect poor prescribing practices as the prescribing software used in Australian primary practice defaults to issuing repeat authorisations for prednisolone. Thus, this may also reflect a flaw in the systems used to support the delivery of primary care in Australia. It is also important to note, because EMRs within Australia only capture prescriptions issued and not the actual quantity dispensed the current data may even overestimate the actual amount of OCSs used.

Like short acting bronchodilators, which are available over the counter in Australia, so too are most medications for allergic rhinitis. As such, this may be a major factor in why this comorbidity was underreported, particularly in EMR. In

acknowledging this, it is also important to note that under recognition of allergic rhinitis may result in inadequate treatment and negative impacts on asthma outcomes.[30–32] To this effect, community pharmacists could be invaluable in educating patients about the impact of allergic rhinitis on their health, and their potential role in identifying inappropriate use of short acting bronchodilators and OCS should also be acknowledged.

Similar to the under recognition of allergic rhinitis, and based on EMR, 53% of patients in the database who were using COPD or asthma medications were doing so without a recorded diagnosis of either condition. The widespread failure to record a diagnosis within EMRs is also reflected in the prevalence of asthma in the current study. Specifically, 1% of the >800,000 patients in the database had active asthma, a figure much lower than the 11% prevalence recorded in the wider Australian population.[2] In this regard, more needs to be done to ensure patients are given an appropriate diagnosis which is documented in the clinical record before commencing ongoing management, including the assessment of lung function as there is often a paucity of these data recorded in general practice. It is also possible that some of these cases where a conclusive diagnosis has not been recorded in the EMR may be a result of patients moving between practices or doctor shopping.

In terms of addressing these issues, this will require recognition of the OCS burden, and establishment of more structured and personalised review processes which includes consultation and review after each severe exacerbation and referral of patients on higher GINA steps with repeated exacerbations to specialist physicians. Additionally, changes to consumer behaviour and OCS prescribing habits along with further defining the diagnostic criteria for asthma and COPD would be beneficial.

The present study also identified a high rate of repeated severe exacerbations in patients with GINA step 1 asthma. This observation raises a number of clinically important questions and requires further investigation to understand why this has occurred. However, it does suggest this subgroup could benefit from a review of their existing management strategies either through regular ICS or as needed anti-inflammatory reliever and less reliance on short acting bronchodilators. There was also a high proportion of patients at GINA step 2 from the total study cohort who had four or more severe exacerbations recorded in their EMR. It is possible this finding could be an artifact of the smaller sample size of the GINA 2 group, compared to other groups, or it may indicate that many of these patients were either under-treated or poorly compliant with their treatment regimen.

Similarly, the high exacerbation rate in patients with GINA 4 and 5a asthma indicates there is greater scope for specialist referral as the existing management strategies are not sufficient in controlling their condition. Likewise, the elevated exacerbation rates in GINA 5b patients indicate ongoing reviews would be beneficial in ensuring treatment adherence with specialist recommendations.

In a recent study examining exacerbations in patients with GINA 4 or 5 asthma, those referred to specialist care were more likely to experience no exacerbations (45.3%), than those who were not referred (17.4%).[19] Collectively, these observations suggest there is potential to reduce the exacerbation burden on Australian adults living with asthma, through regular targeted and personalised reviews, ongoing refinement of existing practices and a shift in management behaviours.

It is also possible that when seeking emergency medical care for an exacerbation, some patients may "doctor shop" and consult the first available physician including emergency rooms and other providers of urgent health care. Meaning the frequency of their exacerbations is higher than their regular physician records in the EMR.

As such, the introduction of an annual structured review process which includes patient reported outcomes to supplement EMR, and to replace the current patient-driven healthcare seeking approach would be effective in improving asthma control.

Conclusion

The present study supports previous observations that exacerbations contribute significantly to the burden of disease and treatment for adult Australians living with asthma. As such, it is not surprising that 8% of patients with ≥GINA 4 treatment intensity asthma experienced ≥2 exacerbations requiring OCS therapy and patients repeatedly exposed to OCS are at an increased risk osteoporosis and sleep apnoea. What was more surprising was the high rate of exacerbations and OCS use experienced by patients who were categorised as GINA step 1. We propose that issuing more than one prescription or a large supply that might treat multiple exacerbations for oral OCS might provide a red flag for GPs to

review the asthma management plans for patients with apparently mild disease in order to reduce the risk of future exacerbations and hence the burden of both the disease and treatment.

Abbreviations

BMI, body mass index; COPD, chronic obstructive pulmonary disease; EMR, electronic medical records; GINA, Global Initiative for Asthma; GERD, gastroesophageal reflux disease; OCS, oral corticosteroids.

Data Sharing Statement

The dataset supporting the conclusions of this article was derived from the Optimum Patient Care Research Database Australia (https://optimumpatientcare.org.au/). The OPCRD has ethical approval from The Royal Australian College of General Practitioners (RACGP) National Research and Evaluation Ethics Committee (NREEC) to hold and process anonymised research data (NREEC Reference: 18-013). This study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee – the independent scientific advisory committee for the OPCRDA. The authors do not have permission to give public access to the study dataset; researchers may request access to OPCRDA data for their own purposes. Access to OCPRDA can be made via the OCPRDA website (https://opcrd.co.uk/our-database/data-requests/) or via the enquiries email info@optimumpatientcare.org.au.

Ethics Approval

The study protocol was established prior to data extraction, in accordance with the criteria for the European Network Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and follows the ENCePP code of conduct (EMA 2014). As noted, the dataset supporting the conclusions of this article was derived from the Optimum Patient Care Research Database Australia (https://optimumpatientcare.org.au/). The OPCRDA has ethical approval from The Royal Australian College of General Practitioners (RACGP) National Research and Evaluation Ethics Committee (NREEC) to hold and process anonymised research data (NREEC Reference: 18-013). Registration of the OPCRDA database and study with the European Union Electronic Register of Post-Authorization studies were also undertaken (EUPAS41161). Approval for this study was granted by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee – the independent scientific advisory committee for the OPCRD (ADEPT0521).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors.

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Disclosure

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References

1. Maddox L, Schwartz DA. The pathophysiology of asthma. *Annu Rev Med*. 2002;53:477–498. doi:10.1146/annurev.med.53.082901.103921
2. Australian Institute of Health and Welfare. Asthma Cat no ACM 38. Canberra: AIHW; 2021 Available from: https://www.aihw.gov.au/reports/chronic-respiratory-conditions/asthma-monitoring-based-on-current-indicators/contents/indicators. Accessed June 23, 2022.
3. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012;12:204. doi:10.1186/1471-2458-12-204
4. Australian Institute of Health and Welfare. 2017. Emergency department care 2016–17: Australian hospital statistics. Health services series no. 80. Cat. no. HSE 194. Canberra: AIHW.
5. Thompson PJ, Salvi S, Lin J, et al. Insights, attitudes and perceptions about asthma and its treatment: findings from a multinational survey of patients from 8 Asia-Pacific countries and Hong Kong. *Respirology*. 2013;18::957–967. doi:10.1111/resp.12137
6. McDonald VM, Hiles SA, Godbout K, et al. Treatable traits can be identified in severe asthma registry and predict future exacerbations. *Respirology*. 2019;24:37–47. doi:10.1111/resp.13389
7. Australian Institute of Health and Welfare. Asthma Cat no ACM 33. Canberra: AIHW; 2021 Available from: https://www.aihw.gov.au/reports/chronic-respiratory-conditions/asthma/contents/deaths. Accessed June 23, 2022.
8. Chung LP, Upham JW, Bardin PG, Hew M. Rational oral corticosteroid use in adult severe asthma: a narrative review. *Respirology*. 2020;25:161–172. doi:10.1111/resp.13730
9. Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018;11:193–204. PMID: 30214247; PMCID: PMC6121746. doi:10.2147/JAA.S176026
10. Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effect in asthmatic patients. *J Allergy Clin Immunol*. 2018;141:110–116. doi:10.1016/j.jaci.2017.04.009
11. Global Initiative for Asthma. The global strategy for asthma management and prevention; 2020 Available from: http://www.globalasthmareport.org. Accessed June 23, 2021.
12. Price D, Fletcher M, van der Molen T. Asthma control and management in 8000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *Prim Care Respir Med*. 2014;24:14009. doi:10.1038/npjpcrm.2014.9
13. Price D, David-Wang A, Cho SH, et al. On behalf of the REcognise Asthma and LInk to Symptoms and Experience (REALISE) Asia Working Group. Time for a new language for asthma control: results from REALISE Asia. *J Asthma Allergy*. 2015;8:93–103. doi:10.2147/JAA.S82633
14. Reddel HK, Sawyer SM, Everett PW, Flood PV, Peters MJ. Asthma control in Australia: a cross-sectional web-based survey in a nationally representative population. *Med J Aust*. 2015;202:492–498. doi:10.5694/mja14.01564
15. Bloom CI, Nissen F, Douglas IJ, et al. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax*. 2018;73:313–320. doi:10.1136/thoraxjnl-2017-210650
16. Baptist AP, Busse PJ. Asthma over the age of 65: all's well that ends well. *J Allergy Clin Immunol*. 2018;6:764–773.
17. D'Amato G, Vitale C, Molino A, et al. Asthma-related deaths. *Multidiscip Respir Med*. 2016;11:37. doi:10.1186/s40248-016-0073-0
18. National Asthma Council. Asthma and COPD medications; 2020. Available from: https://d8z57tiamduo7.cloudfront.net/resources/NAC-Asthma-COPD-Meds-Chart-November-2020-Web.pdf. Accessed September 22, 2021.
19. Ryan D, Heatley H, Heaney LG, et al. Potential severe asthma hidden in UK primary care. *J Allergy Clin Immunol Pract*. 2021;9:1612–1623. doi:10.1016/j.jaip.2020.11.053
20. Price D, Menzies-Gow A, Bachert C, et al. Association between a type 2 inflammatory disease burden score and outcomes among patients with asthma. *J Asthma Allergy*. 2021;29:1173–1183. doi:10.2147/JAA.S321212
21. Australian Bureau of Statistics. 2016. The Australian statistical geography standard (ASGS) remoteness structure. Available from: https://www.abs.gov.au/websitedbs/d3310114.nsf/home/remoteness+structure. Accessed June 3, 2021.
22. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulm Med*. 2017;17:74. doi:10.1186/s12890-017-0409-3
23. Blakey JD, Price DB, Pizzichini E, et al. Identifying risk of future asthma attacks using UK medical record data: a Respiratory Effectiveness Group Initiative. *J Allergy Clin Immunol Pract*. 2017;5:1015–1024. doi:10.1016/j.jaip.2016.11.007
24. Azzi EA, Kritikos V, Peters MJ, et al. Understanding reliever overuse in patients purchasing over-the counter short-acting beta$_2$ agonists: an Australian community pharmacy based survey. *BMJ Open*. 2019;9:e028995. doi:10.1136/bmjopen-2019-028995

25. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. *Rheumatology*. 2011;50:1982–1990. doi:10.1093/rheumatology/ker017
26. Bleecker ER, Menzies-GOW AN, Price DB, et al. Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med*. 2020;201:276–293. doi:10.1164/rccm.201904-0903SO
27. Sweeny J, Patterson CC, Menzies-Gow A, et al. on behalf of the British Thoracic Society Difficult Asthma Network. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the optimum patient care research database and the British thoracic difficult asthma registry. *Thorax*. 2016;71:339–346. doi:10.1136/thoraxjnl-2015-207630
28. Tan R, Cvethovski B, Kritikos V, et al. Management of allergic rhinitis in the community pharmacy: identifying the reasons behind medication self-selection. *Pharm Pract*. 2018;16:1332. doi:10.18549/PharmPract.2018.03.1332
29. Bosnic-Anticevich S, Kritikos V, Carter V, et al. Lack of asthma and rhinitis control in general practitioner-managed patients prescribed fixed dose combination therapy in Australia. *J Asthma*. 2017;55:684–694. doi:10.1080/02770903.2017.1353611
30. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-reported assessment of adherence, rhinitis and smoking in relation to asthma control. *Prim Care Respir Med*. 2009;18:300–305. doi:10.4104/pcrj.2009.00037
31. Price D, Kemp L, Sims E, et al. Observational study comparing intranasal mometasone furoate with oral antihistamines for rhinitis and asthma. *Prim Care Respir Med*. 2010;19:266–273. doi:10.4104/pcrj.2010.00040
32. Lohia S, Schlosser RJ, Soler ZM. Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis. *Allergy*. 2013;68:569–579. doi:10.1111/all.12124
33. National Asthma Council. 2021. Australian Asthma Handbook. Available from: https://www.asthmahandbook.org.au/management/adults. Accessed June 3, 2021.