ORIGINAL ARTICLE

Economic Consequences of the Overuse of Short-Acting ß-Adrenergic Agonists in the Treatment of Asthma in Spain

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Abstract

Objective: To determine the relationship between short-acting ß-adrenergic agonist (SABA) overuse and health care resource use and costs in asthma patients in routine clinical practice.
Methods: A longitudinal retrospective study was conducted in Spanish primary and specialized care centers using the BIG-PAC medical records database. The study population comprised asthma patients ≥12 years of age who attended ≥2 consultations during 2017 and had 1-year follow-up data available. The main outcomes were demographics, comorbidities, medication, and clinical and health care resource use and costs. The relationship between SABA overuse and health care costs and between asthma severity and health care costs was determined.
Results: The SABA use IN Asthma (SABINA) study included 39 555 patients, with a mean (SD) age of 49.8 (20.7) years (64.2% female). The Charlson comorbidity index was 0.7 (1.0). SABA overuse (≥3 canisters/y) was 28.7% (95%CI, 27.7-29.7), with a mean of 3.3 (3.6) canisters/y. Overall, 5.1% of patients were prescribed ≥12 canisters/y. SABA overuse was correlated with health care costs (ρ=0.621; *P*<.001). The adjusted mean annual cost/patient according to the Global Initiative for Asthma (GINA 2019) classification of asthma severity was €2231, €2345, €2735, €3473, and €4243 for steps 1-5, respectively (*P*<.001). Regardless of asthma severity, SABA overuse yielded a significant increase in health care costs per patient and year (€5702 vs €1917, *P*<.001) compared with recommended use (<2 canisters/y).
Conclusion: SABA overuse yields high costs for the Spanish National Health System. Costs increased with severity of asthma.

Key words: Short-acting ß-adrenergic agonist. Overuse. Exacerbations. Resource use. Cost.

Resumen

Objetivo: Determinar la relación entre la sobreutilización de agonistas beta adrenérgicos de acción corta (SABA) en pacientes con asma y el uso y coste de recursos sanitarios en la práctica clínica rutinaria.
Métodos: Se realizó un estudio longitudinal retrospectivo en atención primaria y especializada en España, en el que se utilizó la base de datos de registros médicos BIG-PAC®. Se incluyeron pacientes con asma ≥12 años que asistieron a ≥2 consultas durante 2017 y con datos disponibles del seguimiento durante 1 año. Los principales resultados analizados fueron características demográficas, comorbilidades, medicaciones, y el uso y coste de recursos clínicos y sanitarios. Se determinó la relación de los costes sanitarios tanto con la sobreutilización de SABA como con la severidad del asma.
Resultados: Este estudio sobre el uso de SABA en asma (SABINA, del inglés "SABA use IN Asthma") incluyó a 39.555 pacientes, con una edad media (DE, desviación estándar) de 49,8 años (20,7); 64.2% fueron mujeres. La media del índice de comorbilidad Charlson fue 0,7 (1,0). La sobreutilización de SABA (≥3 envases/año) fue del 28,7% (IC95%: 27,7–29,7), con una media global de 3,3 envases (3,6) /año. En total, el 5,1% de los pacientes fueron prescritos con ≥12 envases/año. La sobreutilización de SABA correlacionó con los costes sanitarios ($\rho = 0{,}621$; $p < 0{,}001$). El coste medio anual/paciente según la clasificación de severidad del asma de la *Global Initiative for Asthma* (GINA 2019) fue de 2.231 €, 2.345 €, 2.735 €, 3.473 €, y 4.243 €, para los pasos 1-5, respectivamente ($p < 0{,}001$). Sin considerar la severidad del asma, la sobreutilización de SABA resultó en un incremento significativo de costes sanitarios por paciente y año en comparación con los costes asociados a un uso recomendado (<2 envases/año), (5.702 € vs. 1.917 €, $p < 0{,}001$).
Conclusión: La sobreutilización de SABA conlleva un mayor coste para el sistema sanitario español. Los costes son mayores en relación con la severidad del asma.

Palabras clave: Agonistas beta adrenérgicos de acción corta. Sobreutilización. Exacerbaciones. Uso de recursos. Costes.

Introduction

Asthma is a chronic inflammatory airway disease characterized by bronchial hyperresponsiveness and variable airflow obstruction [1]. In Spain, the prevalence of asthma is around 5%, with differences reported between regions [2]. The goal of asthma management is to achieve symptom control and reduce the risk of exacerbations [1]. However, patients with uncontrolled disease may be at risk of more severe disease owing to poor diagnosis, inadequate clinical evaluation, excessive use of reliever medication because of symptom misperception, and/or poor adherence to treatment [3-8].

Asthma is one of the most common reasons for primary care consultations globally [9]. In Spain, the annual expenditure on visits to primary care has been estimated at between €900 and €1200 million, with an annual cost per patient of €1726, which is higher in people aged ≥65 years and in those with more severe asthma [10]. Asthma places a high economic burden on the Spanish National Health System, patients and their families, and society in general [11,12].

Therapy is usually initiated with a short-acting ß-adrenergic agonist (SABA) for symptomatic relief, although there is uncertainty surrounding the potential risks associated with long-term SABA use, especially in the context of severe exacerbations [13]. The Global Initiative for Asthma (GINA) recommends the use of inhaled corticosteroids (ICS)/formoterol in the management of asthma and stresses the risk of SABA overuse (3-12 canisters/y) in exacerbations [1]. The evidence supporting these recommendations is provided by randomized controlled trials and real-world data. The SYmbicort Given as needed in Mild Asthma (SYGMA) program confirmed the safety and superiority of budesonide/formoterol over reliever therapy with terbutaline as needed in reducing exacerbations and showed that symptom control was similar to that observed with regular maintenance controller therapy with budesonide plus terbutaline as needed [14,15]. These findings were confirmed in 2 open-label studies (START and PRACTICAL) [16,17].

However, despite the availability of more effective treatments for asthma control, patients with mild asthma tend to use SABAs when symptoms worsen owing to the instant relief achieved with no need for long-term therapies [18]. Several reports have highlighted the relationship between SABA overuse and its clinical and economic impact in terms of mortality, adverse effects, and/or exacerbations, leading to an increase in health care resources and costs [13,19-21].

Recently, as part of the SABA use IN Asthma (SABINA) program, a series of retrospective observational studies reported that approximately one-third of patients with mild, moderate, and severe asthma across 5 European countries, including Spain, overused SABA (≥3 SABA canisters/y) [22]. It is also known that the inappropriate prescription of SABA leads to increased disease burden [1,19]. The objective of the present study was to determine the relationship between SABA overuse and the use of health care resources and costs in patients diagnosed according to the GINA classification of asthma severity in usual clinical practice.

Patients and Methods

Design and Study Population

A longitudinal retrospective multicenter study based on secondary data and a review of electronic medical records was carried out as part of the SABINA program. The study population was obtained from the unified health care records of health care providers registered in the BIG-PAC anonymized database. Data were extracted from electronic medical records and complementary databases of the financing/procurement department of the public services of 7 Spanish Autonomous Communities (1.9 million patients). Data were validated and recoded (anonymized/dissociated data), before being exported to the BIG-PAC database. The database was approved, validated, and registered by the European Medicines Agency (http://www.encepp.eu/encepp/search.htm). All data are anonymized (confidentiality of information).

This study was classified by the Spanish Agency for Medicines and Medical Devices as a postapproval study (EPA-OD in Spanish) and subsequently approved by the Research Ethics Committee of Hospital de Terrassa, Barcelona. Records remain confidential in compliance with the Law on the Protection of Personal Data.

Inclusion and Exclusion Criteria

The study population comprised all patients aged ≥12 years with a diagnosis of asthma (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM: J45-J46]) who required medical attention for any reason twice or more during 2017 (from 2017/01/01 to 2017/12/31). The index date was defined as the first date the patient required medical attention. Additional inclusion criteria were participation in the medication prescription program (with a record of daily dose, time interval between doses, and duration of each treatment administered) and data availability for at least 1 year since the index date. Asthma patients with a history of pulmonary tuberculosis, pulmonary fibrosis, and/or lung cancer were excluded, as were patients transferred to other centers and patients with end-stage disease.

Demographic, Clinical, and Comorbidity Variables

The demographic, clinical, and comorbidity variables collected were age, sex, time since initial diagnosis (years), body mass index (BMI), smoking habit, forced expiratory volume in the first second (FEV_1, % predicted), eosinophil count (cells/μL), and any history of comorbidities (hypertension, diabetes mellitus, dyslipidemia, obesity, ischemic heart disease, stroke, heart failure, kidney failure, chronic obstructive pulmonary disease, atopic dermatitis, allergic rhinitis, and nasal polyposis). The Charlson comorbidity index [23] for severity (categories: 0, 1, 2, and ≥3) and number of comorbidities were used as summary variables for general comorbidity.

Definition of Asthma and Exacerbations

Records of patients diagnosed with asthma were obtained using the ICD-10 (Code J45-J46). Exacerbations were defined according to the ALERTA-2 guidelines [24] as an event in the

natural course of the disease characterized by exacerbation and identified by a progressive increase in dyspnea, wheezing, cough, and chest tightness, or a combination of all these symptoms, caused by intense airflow obstruction. Severe exacerbations were defined as the need for hospitalization. Moderate/mild exacerbations were events requiring additional treatment (oral corticosteroids [OCS]) to prevent progression (including outpatient or emergency department treatment).

Medications Administered

Data on medications were obtained from the Anatomical Therapeutic Chemical (ATC) classification system [25]. Treatment duration was determined, and the source of the prescription (primary care or specialist care) was collected. The information was obtained from pharmacological prescription records. Patients were treated according to standard clinical practice. Appropriate use of SABAs (R03AC) was defined as <3 prescribed canisters/y; SABA overuse was defined as ≥3 prescribed canisters/y. The distribution of the number of SABA canisters was reported. To calculate ICS use, the inhaled medication prescribed during follow-up was recorded. Since the use of ICS is recommended based on clinical judgment, the criteria used to classify ICS use were as follows: (*a*) dosing schedule (1 inhalation/12 hours) in devices with 120 inhalations, with underuse considered <5 canisters/y and recommended use 5-7 canisters/y; (*b*) dosing schedule (2 inhalations/12 h) in devices with 120 inhalations, with underuse considered <10 canisters/y and recommended use considered 10-14 canisters/y. For other dosing schedules or device presentations, a similar conversion was made assuming the same dosage. Patients were classified at each GINA stage based on the medication prescribed and the dose of ICS prescribed at the index date.

Other Respiratory Medications and Nonrespiratory Medications

We recorded the use of OCS (H02AB), ICS/long-acting ß2 agonists (LABAs) (R03AK), short-acting anticholinergics (SAAC, R03BB), long-acting anticholinergics (LAAC, R03BB04), systemic ß2 agonists (xanthines, R03), leukotriene receptor antagonists (R03DC), biological drugs, home oxygen, and systemic antibiotics (J01). Patients receiving long-term oral/systemic corticosteroid therapy were also differentiated from patients receiving short-term therapy to stabilize exacerbations/flares. The absolute and relative scheduled doses of ICS were classified as low, medium, or high per day, according to GINA [1]. OCS/systemic corticosteroid therapy was considered short-term and aimed at stabilizing exacerbations when the prescription did not exceed 7-15 days. Data were collected on the following medications: acetylsalicylic acid (B01AC06), proton pump inhibitors (A02BC), ß-blockers (C07), anti-inflammatory and antirheumatic drugs (M01), and antihistamines (R06A). Long-term use of OCS was recorded separately.

Resource Use and Costs

Direct health care costs (medical visits [primary care and specialist visits], days of hospitalization, emergency department visits, diagnostic or therapeutic procedures, and pharmaceutical prescriptions) and indirect non–health care costs (productivity lost, days of work lost) were collected. Costs were expressed as the mean cost per patient (mean/patient) during the study period. Unit costs considered in this study are detailed in Supplementary Table S1. Medication cost and cost of days of work lost by each patient, as well as unit costs associated with nonpharmacologic resource use (eg, visits and inpatient stays), were also retrieved from the real-world costs published by Sicras-Mainar et al [12]. Medical prescriptions were quantified according to the public retail price + value added tax per container at the time of prescription (according to Bot Plus, General Council of Associations of Official Pharmacists of Spain; https://botplusweb.portalfarma.com/). Days of work lost were evaluated as indirect costs, according to the mean interprofessional salary (source: Spanish National Statistics Institute [Instituto Nacional de Estadística]) [26].

Statistical Methods

A descriptive univariate statistical analysis was performed. Qualitative data were expressed as absolute and relative frequencies and quantitative data as mean (SD). The 95%CI of estimated parameters was based on the total number of patients with nonmissing values. In the bivariate analysis, the ANOVA, χ^2 test, and Spearman correlation were used.

A multiple linear regression analysis (stepwise in ≤0.05/out ≥0.10) was performed to determine the relationship between SABA overuse (independent variable) and health care costs (dependent variable) adjusted for covariates. The covariates included were sex, age, time since diagnosis, and general comorbidity (Charlson index), which was considered an ordinal variable with incremental values from 0 to 37, as well as asthma severity (GINA) [1], which was considered an ordinal variable with incremental values from 1 to 5, and previous exacerbations.

An ANCOVA model (procedure: marginal means, Bonferroni-adjusted) was used to determine the relationship between asthma severity (GINA) [1] (independent variable) and health care costs (dependent variable) adjusted for covariates. The covariates finally selected in the ANCOVA model were age, FEV_1, general comorbidity (Charlson index), and time since diagnosis.

Nonparametric methods (central limit theorem) were used because of the large sample size (nearly 40 000 patients) and in order to facilitate interpretation of results (eg, avoiding transformation of variables). This approach is asymptotically valid as sample sizes increase [27], with the central limit theorem–based methods providing at least as accurate an estimate of standard errors as, for example, the bootstrap approach [28]. Statistical significance was set at $P<.05$. The analysis was conducted using SPSS for Windows, Version 23 (IBM Corp).

Results

Of an initial population of 850 684 patients who required care during the inclusion period, 44 663 were diagnosed with asthma (prevalence, 5.3% [95%CI, 5.1-5.5]). Of these,

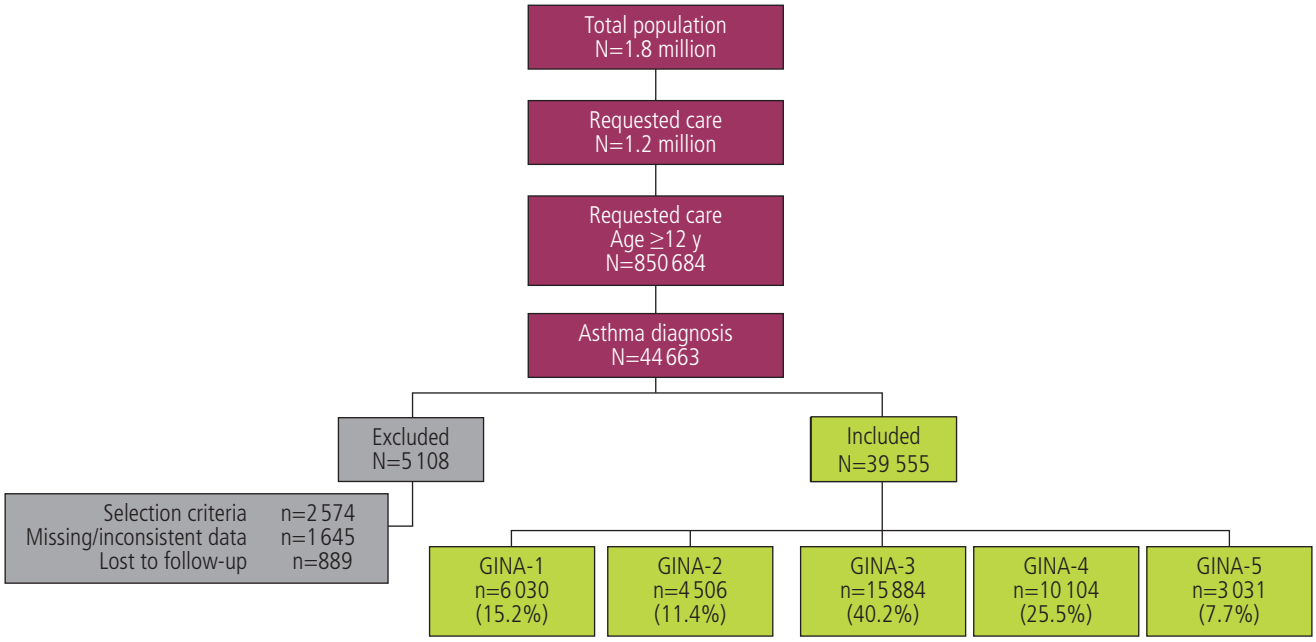

Figure 1. Study flow chart. GINA indicates Global Initiative for Asthma.

39 555 patients who met the selection criteria were analyzed and followed up during the study period (Figure 1). The mean age of patients was 49.8 years, 64.2% were female, and the mean (SD) Charlson comorbidity index was 0.7 (1.0) (Table 1). During the 12-month follow-up, concomitant medication was prescribed to 70.1% of patients (Table 2). Nonsteroidal anti-inflammatory drugs (35.8%) and antihistamines (35.0%) were the most commonly prescribed medications. Asthma-related medication included long-term OCS (>6 months), which were prescribed to 5.1% of patients, and leukotriene receptor antagonists and home oxygen therapy, which were prescribed to 27.1% and 2.9% of patients, respectively. Only 0.3% of patients used biological drugs.

According to the GINA classification of asthma severity (steps 1 to 5) [1], the study groups were distributed as follows: 15.2%, 11.4%, 40.2%, 25.5%, and 7.7%, respectively (P<.001, Table 3). Most comorbidities increased according to the GINA classification step. SABA overuse (≥3 prescribed canisters/y) was recorded in 28.7% of patients (95%CI, 27.7%-29.7%), with a mean (SD) of 3.3 (3.6) canisters/y. According to the GINA classification, these percentages were 25.4%, 17.3%, 26.4%, 33.4%, and 48.7% (P<.001), respectively. Overall, 5.1% of patients were prescribed ≥12 canisters/y.

ICS were underused in 13.4% of patients (Table 3). Starting from step 2 of the GINA classification, these percentages were 17.1%, 15.8%, 9.9%, and 7.0% (P<.001), respectively. Furthermore, while recommended ICS use increased across the GINA steps, underuse decreased. The percentage of patients with at least 1 exacerbation was 45.0% (according to GINA, from steps 1 to 5: 39.7%, 34.5%, 44.3%, 49.5%, and 59.8%, respectively; P<.001). The mortality rate due to asthma was 1.3%, increasing according to GINA severity (0.3%, 0.8%, 1.0%, 1.7%, and 4.2%, respectively, P<.001).

Gross and adjusted resource use and costs during the follow-up by GINA steps are shown in Table 4. The annual mean (SD) number of visits was 9.3 (10.8) for primary care, 1.5 (1.8) for specialist care, and 0.8 (1.1) for the emergency department. The mean length of hospital stay was 2.9 (4.1) days. The mean (SD) annual productivity loss (indirect costs) due to asthma was 3.8 (19.8) days. The percentage of patients hospitalized during follow-up was 14.1%, which increased according to GINA severity (9.8%, 7.7%, 13.4%, 18.3%, and 22.7%, respectively, P<.001).

Of the total costs generated by asthma patients included in the study, 87% corresponded to direct health care costs and 13% to indirect costs (productivity loss), with a total annual mean (SD) cost of €3001 (€3312) per patient (Table 4). The major cost drivers were inpatient stays (40.6%), associated medication (23.9%), loss of productivity (13%), and primary care visits (7.2%). Total costs increased according to GINA severity, with the mean annual cost per patient with asthma adjusted for covariates (ANCOVA) being €2231, €2345, €2735, €3473, and €4243, respectively (P<.001). Between-step differences were maintained for direct health care costs. Indirect costs (loss of productivity), although high, did not differ significantly.

In the binary Spearman ordinal correlation model, SABA overuse correlated with exacerbations (ρ=0.792; P<.001) and health care costs (ρ=0.621; P<.001), and exacerbations correlated with total cost (ρ=0.809; P<.001). In the adjusted multiple linear regression model, SABA overuse was associated with higher health care costs (β=0.479; P<.001).

Figure 2 and Supplementary Table S2 show the total costs per patient according to overuse and recommended use of SABA, underuse and recommended use of ICS, and exacerbations during the follow-up period by study group.

Table 1. Baseline Characteristics of Patients

Demographic characteristic	N=39 555
Mean (SD) age, y	49.8 (20.7)
Sex (female), (%)	64.2
Other variables, mean (SD)	
Time since diagnosis, y	28.0 (9.3)
FEV_1, % of theoretical	72.1 (9.5)
BMI, kg/m^2	28.0 (6.5)
Eosinophils, cells/mL	300.4 (146.6)
General comorbidity, mean (SD)	
Number of diagnoses	2.6 (2.0)
Charlson comorbidity index score	0.7 (1.0)
Associated comorbidities, %	
Hypertension	28.4
Diabetes mellitus	11.1
Dyslipidemia	31.0
Obesity	27.7
Active smoking	11.2
Ischemic heart disease	4.2
Cerebrovascular accident	3.0
Heart failure	4.3
Kidney failure	2.5
COPD	9.7
Atopic dermatitis	34.5
Allergic rhinitis	55.7
Chronic rhinosinusitis with nasal polyps	11.0

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second.

Table 2. Use of Asthma-Associated and Concomitant Medication in Patients With Asthma

Use of asthma-associated medication, %	N=39 555
Oral corticosteroids	26.3
Oral corticosteroids, long-term use (>6 mo)	5.1
Systemic antibiotics	14.8
Inhaled corticosteroids	11.4
ICS/LABA	73.4
Short-acting anticholinergics	4.7
Systemic ß2 agonists (xanthines)	3.2
Leukotriene receptor antagonists	27.1
Biological drugs	0.3
Home oxygen therapy	2.9
Concomitant medication, %	
Acetylsalicylic acid	6.6
Proton-pump inhibitor	30.5
ß-Blockers	7.1
Nonsteroidal anti-inflammatory drugs	35.8
Antihistamines	35.0
Mean (SD) concomitant medication	1.1 (1.0)
Use of concomitant medication, %	
0	29.9
1	37.4
2	22.4
≥3	10.3

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting ß2 agonist.

As observed, total costs increased according to GINA severity with SABA overuse, in the context of ICS underuse, and when patients presented with exacerbations.

In summary, patients who overused SABAs had a significantly higher mean number of exacerbations during the 1-year follow-up (1.9 vs 0.2; *P*<.001), higher mortality rates (2.5% vs 0.8%; *P*<.001), and increased health care costs (€5702 vs €1917; *P*<.001). Additionally, underuse of ICS, compared with recommended use, was associated with a higher exacerbation rate (1.2 vs 0.6; *P*<.001 [unadjusted model]) and an increase in health care costs (€4116 vs €2902; *P*<.001 [unadjusted model]).

Discussion

The goals of asthma treatment are to control symptoms and to minimize the risk of exacerbations. ICS control airway inflammation, thus making them the cornerstone of asthma management [1]. However, our results confirm notable overuse of SABAs in asthma patients in Spain, with almost one-third of patients being prescribed ≥3 canisters/y. Notably, 5.1% of patients were prescribed ≥12 canisters/y. These results suggest that SABA overuse is associated with increased health care resource use and costs. Similarly, underuse of ICS also generates higher costs. Total costs increased with each GINA severity step. The mean total cost per patient was €3001. The major cost drivers were hospital admissions (40.6%), associated medication (23.9%), and productivity loss (13%). While total and direct costs increased significantly with each GINA step, loss of productivity did not differ significantly between steps.

In 2010, Welsh and Cates [29] estimated that nearly one-third of adult patients with asthma overused SABAs and that 5.1% were prescribed an excessive number of SABA canisters (≥12 canisters/y). Similar results have been reported for children [21,30]. Importantly, frequent use of SABAs has been identified as a key indicator of poor asthma control [31], and the use of ≥3 inhalers/y in asthma has been associated with a 2-fold increase in the risk of hospitalization or emergency department visits [32]. Indeed, as reported by FitzGerald et al [19] and in accordance with our results, inappropriate use of SABAs remains problematic in a significant percentage of asthma patients and is associated with increased use of medical

Table 3. SABA Overuse (Defined as ≥3 Canisters/y), ICS Use, and Description of Exacerbations and Mortality During the Follow-Up Period by Study Group

Study group	GINA–1	GINA–2	GINA–3	GINA–4	GINA–5	Total	*P* Value
Patients, No. (%)	6030 (15.2)	4506 (11.4)	15 884 (40.2)	10 104 (25.5)	3031 (7.7)	39 555 (100)	<.001
Use of SABA							
Mean (SD) canisters/y	2.5 (2.1)	2.7 (2.6)	3.1 (3.4)	3.9 (4.4)	5.0 (4.1)	3.3 (3.6)	
SABA ≥3 canisters/y, %	25.4	17.3	26.4	33.4	48.7	28.7	<.001
SABA ≥12 canisters/y, %	1.0	2.4	4.3	8.0	11.6	5.1	
Use of ICS, %							
Underuse	---	17.1	15.8	9.9	7.0	13.4	<.001
Recommended use	---	78.1	80.9	85.8	88.8	82.7	
Overuse	---	4.7	3.3	4.3	4.1	3.9	
Previous exacerbations (1 y), %	50.4	45.8	52.8	56.3	64.1	53.5	
Follow-up period (1 y)							
Patients with exacerbations, %	39.7	34.5	44.3	49.5	59.8	45.0	<.001
Mean (SD) exacerbations	0.6 (0.9)	0.5 (0.8)	0.7 (0.9)	0.8 (1)	1.1 (1.1)	0.7 (0.9)	
Exacerbations/year, %							
0	60.3	65.5	55.7	50.5	40.2	55.0	
1	23.9	23.6	24.9	24.8	24.2	24.5	
2	9.8	7.5	13.1	17.5	22.3	13.8	
≥ 3	5.9	3.5	6.3	7.2	13.3	6.7	
Patients with exacerbations, %							
Mild-moderate	39.7	34.3	44	48.8	59.4	44.6	
Severe (hospital admission)	9.8	7.7	13.4	18.3	22.7	14.1	
Mortality (asthma-related), %	0.3	0.8	1.0	1.7	4.2	1.3	<.001

Abbreviations: GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; SABA, short-acting ß2 agonist.

care and a higher risk of adverse outcomes. The excessive use of SABAs and the fluctuating character of asthma may be due, in part, to the fact that patients are often unaware that their disease is uncontrolled, despite presenting with symptoms and exacerbations. SABAs used as needed for symptom relief, together with the natural tendency of patients to seek immediate symptom relief, may direct more attention toward symptom management rather than toward treating the underlying inflammation inherent in asthma, potentially leading to overreliance on SABAs [33,34]. Therefore, SABAs may need to be restricted or combined with an alternative treatment in patients with a confirmed asthma diagnosis, although additional data are needed to ensure that this approach has an impact on routine clinical practice. In this sense, the GINA recommends the fixed ICS/formoterol combination as needed as the preferred reliever therapy at all asthma steps [1]. Cumulative data from trials and real-world studies confirmed the higher efficacy of ICS/formoterol on demand in the prevention of asthma exacerbations compared with reliever therapy plus SABAs as needed [35]. These data, together with the lack of anti-inflammatory action of SABAs as initial treatment in mild asthma and the increased risk of exacerbations associated with SABA overuse, place the combination of ICS/formoterol in an advantageous therapeutic position in terms of overuse of SABA monotherapy, adverse effects, and costs. Nevertheless, shared decision-making between patient and physician should consider not only the available pharmacological repertoire, but also other clinical and nonclinical features, such as the patient's characteristics, needs, goals, and preferences, as well as asthma activity and control, education on inhalation technique, comorbidities, modifiable risk factors, environmental control, and adherence to treatment [36].

Patients overusing SABAs had more annual exacerbations and generated higher annual health care costs than those who followed recommended dosing. Indeed, some studies have shown that SABA overuse is a risk factor for exacerbations [37], mortality [38], and health care resource use [38-40]. Notably, the UK National Review of Asthma Deaths [40] found that 39% of people who died of asthma had been prescribed ≥12 SABA inhalers in the year before their death.

In line with our findings, a systematic review by Puig-Junoy et al [39], found that the highest costs were associated with hospitalizations, medications, and medical visits. Furthermore, health care costs also increased with the level of severity. A Canadian review underlined the high consumption of resources in hospitalizations, emergency visits, medical visits, and medication generated by asthma [41]. However, the lack of studies on SABA overuse makes comparisons difficult. Recent reports from the SABINA program [22] have shown that the prevalence of SABA overuse was 9% in Italy, 16% in Germany, 29% in Spain, 30% in Sweden, and 38% in the United Kingdom. Most studies and clinical practice guidelines have concluded that approximately 70% of the cost of asthma (hospitalization, emergency visits) is attributable to poor asthma control. Therefore, strategies aimed at generating cost savings should include greater use of preventive medication, especially inhaled corticosteroids, and improved patient education [1,11,42].

Our study is limited by our categorization of asthma and a possible bias in patient classification, the selection of

Table 4. Resource Use and Direct Healthcare Costs and Indirect Costs During Follow-Up (1 y): Raw and Adjusted Costs by GINA Step

GINA Step	GINA–1	GINA–2	GINA–3	GINA–4	GINA–5	Total
Patients, No. (%)	6030 (15.2)	4506 (11.4)	15 884 (40.2)	10 104 (25.5)	3031 (7.7)	39 555 (100)
Resources use						
Medical visit						
Mean (SD) no. of primary care visits	7.9 (9.5)	9.2 (10.5)	8.7 (10.1)	10.2 (11.6)	12.3 (13.1)	9.3 (10.8)
Mean (SD) no. of specialist care visits	1.2 (1.7)	1.1 (1.6)	1.4 (1.6)	1.7 (2.0)	2.4 (2.4)	1.5 (1.8)
Mean (SD) no. of emergency department visits	0.7 (1.0)	0.6 (1.0)	0.8 (1.1)	0.9 (1.1)	1.2 (1.3)	0.8 (1.1)
Mean hospital stay, d	2.4 (3.6)	2.1 (3.6)	2.7 (3.8)	3.4 (4.5)	4.3 (4.9)	2.9 (4.1)
Hospitalized patients, %	9.8	7.7	13.4	18.3	22.7	14.1
Mean (SD) no. (%) of supplementary tests						
Laboratory tests	1.1 (1.6)	1.2 (1.7)	1.3 (1.7)	1.4 (1.9)	1.8 (2.1)	1.3 (1.8)
Conventional radiology	0.1 (0.4)	0.1 (0.4)	0.1 (0.5)	0.2 (0.6)	0.3 (0.5)	0.2 (0.5)
Diagnostic/therapeutic tests	1.9 (1.2)	1.8 (1.1)	2.1 (1.3)	2.3 (1.4)	2.8 (1.5)	2.1 (1.3)
Mean lost productivity, d	3.7 (17.2)	4 (20.7)	3.8 (19.6)	4 (19.5)	4 (24.5)	3.8 (19.8)
Costs (€ per patient)						
Medical visit						
Mean (SD) no. of primary care visits	182 (220)	214 (244)	202 (235)	237 (270)	286 (303)	216 (250)
Mean (SD) no. of specialist care visits	111 (158)	103 (148)	125 (151)	157 (184)	223 (220)	136 (170)
Mean (SD) no. of emergency department visits	82 (117)	70 (116)	92 (130)	105 (132)	140 (158)	95 (130)
Mean (SD) hospital stay, d	995 (1513)	903 (1508)	1,137 (1595)	1,442 (1901)	1,820 (2072)	1,219 (1716)
Mean (SD) no. of supplementary tests						
Laboratory tests	24 (36)	27 (38)	29 (39)	30 (41)	41 (46)	30 (40)
Conventional radiology	2 (8)	2 (8)	3 (9)	4 (11)	5 (9)	3 (9)
Computed tomography	2 (16)	2 (24)	2 (17)	4 (31)	9 (47)	3 (25)
Magnetic resonance imaging	0 (5)	1 (10)	0 (6)	1 (10)	1 (15)	0 (9)
Diagnostic/therapeutic tests	69 (44)	68 (42)	77 (47)	84 (53)	103 (55)	78 (49)
Mean (SD) no. of pharmaceutical prescriptions						
Other concomitant medication	102 (95)	108 (96)	115 (99)	117 (101)	158 (104)	116 (100)
Other asthma associated medication	149 (128)	410 (173)	643 (176)	1021 (194)	1670 (1022)	717 (513)
Mean (SD) health costs, €	1718 (2020)	1910 (2032)	2424 (2155)	3202 (2579)	4456 (2993)	2612 (2425)
Mean (SD) indirect costs (productivity loss), €	371 (1745)	407 (2097)	380 (1986)	403 (1977)	400 (2477)	389 (2005)
Mean (SD) total costs, €	2088 (2871)	2317 (3090)	2805 (3093)	3605 (3422)	4856 (4021)	3001 (3312)
Mean (95%CI) adjusted costs per patient (€) (ANCOVA)						
Direct health care costs	1898 (1841-1955)	1981 (1914-2047)	2368 (2332-2404)	3079 (3034-3125)	3837 (3751-3922)	
Indirect costs (productivity loss)	333 (280-385)	364 (303-424)	366 (333-399)	394 (352-435)	406 (328-485)	
Total costs	2231 (2149-2312)	2345 (2249-2440)	2735 (2683-2786)	3473 (3408-3538)	4243 (4120-4366)	

Abbreviation: GINA, Global Initiative for Asthma.

the therapeutic groups, and cost measures. However, these limitations are attributable to the information system. Other limitations are inherent to the observational retrospective design of our study and include disease underreporting (ie, not all asthma patients were identified), differences in disease management among health care professionals, possible inaccuracy of diagnostic coding and other comorbidities, and the lack of variables that could influence results (eg, socioeconomic level, work exposure). Possible confounding variables affected the study variables equally. Potential sources of bias include the classification of patients by GINA severity according to the medication prescribed (although such a bias might affect all groups similarly) and the percentage of medicated patients not recorded in the database (eg, private hospitals outside the public health system, private purchase of medicine) and therefore not included. However, most patients, even those treated in private care, obtained prescriptions from the public health system to reduce costs. In addition, we could not ensure that canisters collected from the pharmacy were actually used, as patients frequently collect several SABA canisters for potential use in different everyday scenarios (eg, at home, in the car, at work). However, this does not mean that they overuse them. Lastly, direct non–health care costs (out-of-pocket costs or costs paid by the patient/family) were not considered, since they were not recorded in the database and no access to patients was established in the study design. Of note,

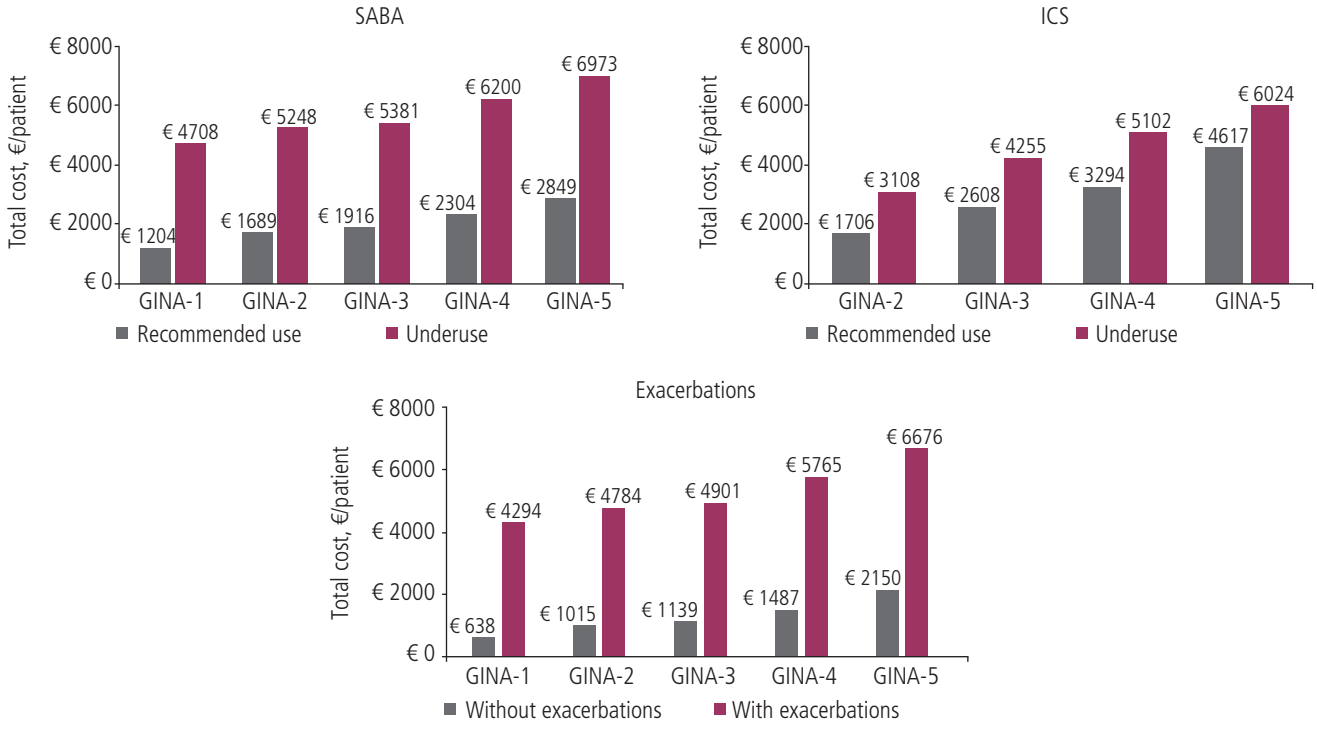

Figure 2. Total costs (euros) per patient over the study period (1 year) according to overuse and recommended use of SABAs (A), underuse and recommended use of ICS (B), and exacerbations (C). GINA indicates Global Initiative for Asthma; ICS, inhaled corticosteroids; SABA, short-acting ß2 agonist.

the lack of adequate standardization of the methodologies used means that the results of this study and their external validity should be addressed with caution.

Our objective was to promote appropriate treatment management that can be replicated in other health institutions with the aim of improving the quality of life of people with asthma and their capacity to perform their activities of daily living. More real-life studies are needed to assess the true impact of asthma treatments on the less severe stages of the disease.

In conclusion, this study shows that mean unit cost increases according to the GINA asthma severity classification step and highlights the relationship between SABA overuse, increased resource use, and higher direct and indirect health care costs due to loss of productivity.

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Conflicts of Interest

During the 3 years prior to this study, A. Valero received honoraria for speaking engagements at meetings sponsored by AstraZeneca, Boehringer-Ingelheim, MSD, and Chiesi and travel assistance for attending meetings from AstraZeneca, Chiesi, and Novartis. He has also acted as a consultant for ALK, AstraZeneca, Boehringer, MSD, MundiPharma, and Sanofi and received grants from government agencies and not-for-profit foundations, as well as from AstraZeneca, Chiesi, and Menarini.

V. Plaza has received honoraria for speaking engagements at meetings sponsored by AstraZeneca, Boehringer-Ingelheim, MSD, and Chiesi in the last 3 years. He has also received travel assistance for attending meetings from AstraZeneca, Chiesi, and Novartis. He has acted as a consultant for ALK, AstraZeneca, Boehringer, MSD, MundiPharma, and Sanofi and received funding/grant support for research projects from a variety of government agencies and not-for-profit foundations, as well as from AstraZeneca, Chiesi, and Menarini.

J. Molina has received honoraria for speaking engagements at meetings sponsored by AstraZeneca, GlaxoSmithKline, Menarini, Novartis, Pfizer, Roche, semFYC, and SERMAS in the last 3 years. He has also received honoraria from the same companies for preparing documents and attending expert meetings.

S. Simón, M. Capel, and J. Nuevo were AstraZeneca employees at the time the study was conducted.

A. Sicras-Navarro and A. Sicras-Mainar were involved in the development of this manuscript as independent consultants.

References

1. The Global Initiative for Asthma (GINA). 2019 GINA report, global strategy for asthma management and prevention.

https://ginasthma.org/reports/2019-gina-report-global-strategy-for-asthma-management-and-prevention/.
2. Vila-Rigat R, Panadès Valls R, Hernandez Huet E, Sivecas Maristany J, Blanché Prat X, Muñoz-Ortiz L, et al. Prevalence of Work-Related Asthma and its Impact in Primary Health Care. Arch Bronconeumol. 2015;51:449-55.
3. Braido F, Baiardini I, Stagi E, Piroddi MG, Balestracci S, Canonica GW. Unsatisfactory asthma control: astonishing evidence from general practitioners and respiratory medicine specialists. J Investig Allergol Clin Immunol. 2010;20:9-12.
4. Quirce S, Plaza V, Picado C, Vennera M, Casafont J. Prevalence of uncontrolled severe persistent asthma in pneumology and allergy hospital units in Spain. J Investig Allergol Clin Immunol. 2011;21:466-71.
5. Aalbers R, Vogelmeier C, Kuna P. Achieving asthma control with ICS/LABA: A review of strategies for asthma management and prevention. Respir Med 2016;111:1-7.
6. Leiria-Pinto P, Carreiro-Martins P, Peralta I, Marques J, Finelli E, Alves C, et al. Factors associated with asthma control in 121 preschool children. J Investig Allergol Clin Immunol. 2021;31(6):471-80.
7. Urrutia I, Delgado J, Domínguez-Ortega J, Mascarós E, Pérez M, Resler G, et al. Clinical Factors Associated With Overuse of Asthma Reliever Medication. J Investig Allergol Clin Immunol. 2020;30:42-8.
8. Barnes PJ, Szefler SJ, Reddel HK, Chipps BE. Symptoms and perception of airway obstruction in asthmatic patients: Clinical implications for use of reliever medications. J Allergy Clin Immunol. 2019;144:1180-6.
9. Finley CR, Chan DS, Garrison S, Korownyk C, Kolber MR, Campbell S, et al. What are the most common conditions in primary care? Systematic review. Can Fam Physician. 2018;64:832-40.
10. Nieto A, Alvarez-Cuesta E, Boquete M, Mazón A, de la Torre F. The cost of asthma treatment in Spain and rationalizing the expense. J Investig Allergol Clin Immunol. 2001;11:139-48.
11. Martínez-Moragón E, Serra-Batllés J, De Diego A, Palop M, Casan P, Rubio-Terrés C, et al. Economic cost of treating the patient with asthma in Spain: the AsmaCost study. Arch Bronconeumol. 2009;45:481-6.
12. Sicras-Mainar A, Capel M, Navarro-Artieda R, Nuevo J, Orellana M, Resler G. Real-life retrospective observational study to determine the prevalence and economic burden of severe asthma in Spain. J Med Econ. 2020;23:492-500.
13. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. 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;55:1901872.
14. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. N Engl J Med. 2018;378:1877-87.
15. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med. 2018;378:1865-76.
16. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. N Engl J Med. 2019;380:2020-30.
17. Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet. 2019;394:919-28.
18. Valero A, Olaguibel J, Delgado J, Plaza V, Álvarez F, Molina J, et al. Dilemmas and New Paradigms in Asthma Management. J Investig Allergol Clin Immunol. 2019;29:15-23.
19. FitzGerald JM, Tavakoli H, Lynd LD, Al Efraij K, Sadatsafavi M. The impact of inappropriate use of short acting beta agonists in asthma. Respir Med. 2017;131:135-40.
20. Hull SA, McKibben S, Homer K, Taylor SJ, Pike K, Griffiths C. Asthma prescribing, ethnicity and risk of hospital admission: an analysis of 35,864 linked primary and secondary care records in East London. NPJ Prim Care Respir Med. 2016;26:16049.
21. Silver HS, Blanchette CM, Kamble S, Petersen H, Letter M, Meddis D, et al. Quarterly assessment of short-acting beta(2)-adrenergic agonist use as a predictor of subsequent health care use for asthmatic patients in the United States. J Asthma. 2010;47:660-6.
22. Janson C, Menzies-Gow A, Nan C, Nuevo J, Papi A, Quint JK, et al. SABINA: An Overview of Short-Acting β(2)-Agonist Use in Asthma in European Countries. Adv Ther. 2020;37:1124-35.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.
24. Rodrigo GJ, Plaza Moral V, Forns SB, Castro-Rodríguez JA, de Diego Damiá A, Cortés SL, et al. ALERTA 2 guidelines. Latin America and Spain: recommendations for the prevention and treatment of asmatic exacerbations. Spanish Pulmonology and Thoracic Surgery Society (SEPAR). Asthma Department of the Latinamerican Thoracic Association (ALAT). Arch Bronconeumol. 2010;46 Suppl 7:2-20.
25. World Health Organization (WHO). The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD).
26. Instituto Nacional de Estadística. Encuesta anual de coste laboral. EACL. Año 2018. https://www.ine.es/prensa/eacl_2018.pdf.
27. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare resources and costs. Health Econ. 2011;20:897-916.
28. Nixon RM, Wonderling D, Grieve RD. Non-parametric methods for cost-effectiveness analysis: the central limit theorem and the bootstrap compared. Health Econ. 2010;19:316-33.
29. Welsh EJ, Cates CJ. Formoterol versus short-acting beta-agonists as relief medication for adults and children with asthma. Cochrane Database Syst Rev. 2010;Cd008418.
30. Butz AM, Ogborn J, Mudd S, Ballreich J, Tsoukleris M, Kub J, et al. Factors associated with high short-acting β2-agonist use in urban children with asthma. Ann Allergy Asthma Immunol. 2015;114:385-92.
31. Paris J, Peterson EL, Wells K, Pladevall M, Burchard EG, Choudhry S, et al. Relationship between recent short-acting beta-agonist use and subsequent asthma exacerbations. Ann Allergy Asthma Immunol. 2008;101:482-7.
32. Stanford RH, Shah MB, D'Souza AO, Dhamane AD, Schatz M. Short-acting β-agonist use and its ability to predict future

asthma-related outcomes. Ann Allergy Asthma Immunol. 2012;109:403-7.
33. Beasley R, Bird G, Harper J, Weatherall M. The further paradoxes of asthma management: time for a new approach across the spectrum of asthma severity. Eur Respir J. 2018;52:1800694.
34. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? Eur Respir J. 2017;50:1701103.
35. Hatter L, Bruce P, Braithwaite I, Holliday M, Fingleton J, Weatherall M, et al. ICS-formoterol reliever versus ICS and short-acting β(2)-agonist reliever in asthma: a systematic review and meta-analysis. ERJ Open Res. 2021;7:00701-2020.
36. Blanco Aparicio M, Delgado Romero J, Molina París J, Tomás Gómez J, Gómez Ruiz F, Álvarez Gutiérrez FJ, et al. Referral Criteria for Asthma: Consensus Document. J Investig Allergol Clin Immunol. 2019;29:422-30.
37. Patel M, Pilcher J, Munro C, Hosking A, Pritchard A, Shaw D, et al. Short-acting β-agonist use as a marker of current asthma control. J Allergy Clin Immunol Pract. 2013;1:370-7.
38. Suissa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the risk of fatal or near-fatal asthma. Eur Respir J. 1994;7:1602-9.
39. Puig-Junoy J, Pascual-Argenté N. Socioeconomic Costs of Asthma in the European Union, United States and Canada: A Systematic Review. Rev Esp Salud Publica. 2017;91:e201703025.
40. Royal College of Physicians. Why Asthma Still Kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry report. https://www.asthma.org.uk/globalassets/campaigns/nrad-full-report.pdf
41. Ismaila AS, Sayani AP, Marin M, Su Z. Clinical, economic, and humanistic burden of asthma in Canada: a systematic review. BMC Pulm Med. 2013;13:70.
42. Huang YJ, Marsland BJ, Bunyavanich S, O'Mahony L, Leung DY, Muraro A, et al. The microbiome in allergic disease: Current understanding and future opportunities-2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology. J Allergy Clin Immunol. 2017;139:1099-110.

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