Economic consequences of the overuse of short-acting beta-adrenergic agonists (SABA) in the treatment of asthma in Spain

Running title: Costs of SABA overuse in asthma

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Abstract

Objective: To determine the relationship between short-acting beta-adrenergic agonist (SABA) overuse and healthcare resource use and costs in asthma patients in routine clinical practice.

Methods: A longitudinal retrospective study in Spanish primary and specialized care using the BIG-PAC® Medical Records Database was conducted. Asthma patients ≥12 years of age who attended ≥ 2 consultations during 2017 and had 1-year follow-up data available were included. Main outcomes were demographics, comorbidities, medication, clinical and healthcare resource use and costs. The relationship between SABA overuseand healthcare costs, and between asthma severity and healthcare costs was determined.

Results: This SABA use IN Asthma (SABINA) study included 39,555 patients, mean (standard deviation, SD) age 49.8 (20.7) years; 64.2% were female. Charlson comorbidity index was 0.7 (1.0). SABA overuse (≥ 3 canisters/year) was 28.7% (95% CI: 27.7–29.7), with an overall mean number of 3.3 (3.6) canisters/year. Overall, 5.1% of patients were prescribed ≥12 canisters/year. SABA overuse was correlated with healthcare costs ($\rho = 0.621$; $p < 0.001$).The adjusted mean annual cost/patient, according to the Global Initiative for Asthma (GINA 2019) classification of asthma severity, was €2,231, €2,345, €2,735, €3,473, and €4,243,for GINA steps 1−5, respectively ($p < 0.001$). Regardless of asthma severity, SABA overuse yielded a significant increase in healthcare costs per patient and year (€5,702 *vs*. €1,917, $p < 0.001$) compared with recommended use (< 2 canisters/year).

Conclusion: SABA overuse yields greater costs for the Spanish National Health System. Costs increased according to asthma severity.

Key words: Short-acting beta-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 Charlsonfue 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 pacientesfueron prescritos con ≥ 12 envases/año. La sobreutilización de SABA correlacionócon los costes sanitarios ($\rho = 0,621$; $p < 0,001$). El coste medio anual/paciente según la clasificación de severidad del asma de la *Global InitiativeforAsthma* (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€, $p < 0.001$).

Conclusiones: 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 betaadrenérgicos 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, poor diagnosis, inadequate clinical evaluation, excessive use of reliever medication because of symptom misperception, and/or poor treatment adherence are factors that may lead to a proportion of uncontrolled patients being at risk of more severe disease progression [3-8].

Asthma is one of the most common reasons for primary care consultations globally [9]. In Spain, the annual expenditure has been estimated at between €900 and €1,200 million, with an annual cost per patient of approximately €1,726, 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 beta-adrenergic agonist (SABA) for symptom relief, but 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/year) with respect to exacerbations [1]. The evidence supporting these recommendations was 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 versus reliever therapy with terbutaline as-needed alone in reducing exacerbations, and a similar symptom control when compared with regular maintenance controller therapy with budesonide plus terbutaline as-needed [14, 15]. These findings were confirmed intwo 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 SABA when symptoms worsen due to the achieved instant relief with no need of long-term therapies [18]. Several reports have highlighted the relationship between SABA overuse and it's clinical and economic impact in terms of mortality, adverse effects and/or exacerbations, leading to an increase in healthcare 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 mild, moderate, and severe asthma patients across five European countries, including Spain overused SABA (≥ 3 SABA canisters/year) [22]. It is also known that the inappropriate prescription of SABA leads to an increased disease burden[1, 19]. The objective of the study was to determine the relationship between SABA overuse and the use of healthcare resources and costsin patients diagnosed according to the GINA classification of asthma severity, in usual clinical practice.

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Material and Methods

Design and study population

A longitudinal retrospective multicenter study, using secondary data, based on a review of electronic medical records (EMR) was carried out as part of the SABINA program. The study population was obtained from the unified healthcare records of healthcare providers contained in the BIG-PAC®anonymized database. Data were extracted from EMRs and complementary databases of the financing/provision of public services of seven Spanish Autonomous Communities including 1.9 million patients. Data were subjected to validation and recoding (anonymized/dissociated data) and then 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 Health Products asa post-approval study (EPA-OD in Spanish) and subsequently approved by the Research Ethics Committee of the Hospital de Terrassa (Barcelona). Records are kept confidential in compliance with the Law on the Protection of Personal Data.

Inclusion and exclusion criteria

All patients aged ≥12 years with a diagnosis of asthma according to the International Classification of Diseases (ICD-10-MC: J45-J46), who required medical attention for any reasontwice or more during 2017 (from 2017/01/01to 2017/12/31), were included (index date was defined as the first date the patient required medical attention). Additional inclusion criteria wereinclusion 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 sincethe index date. Asthma patients with a history of pulmonary tuberculosis, pulmonary fibrosis and/or lung cancer,patients transferred to other centers, and patients withend-stage diseasewere excluded.

Demographic, clinical and comorbidity variables

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

Definition of asthma and exacerbations

Records of patients diagnosed with asthma were obtained using ICD-10-MC: Code J45-J46. Exacerbations were defined according to the ALERTA-2[24]guidelines as an event in the natural course of the disease characterized by disease exacerbation and identified

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by a progressive increase in difficulty in breathing, a feeling of shortness of breath, 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 room 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 SABA (R03AC) was defined as <3 prescribed canisters/year and SABA overuse was defined as ≥ 3 prescribed canisters/year. Distribution of the number of SABA canisters was described. To calculate ICS use, the inhaled medication prescribed during follow-up was recorded. Since the recommended use of ICS is based on clinical judgment, the following criteria were used to classify ICSuse: a) dosing schedule (1 inhalation/12 hours) in devices with 120 inhalations: underuse (<5 canisters/year), recommendeduse (5−7 canisters/year); b) dosing schedule (2 inhalations/12 hours) in devices with 120 inhalations: underuse (<10 canisters/year), recommendeduse (10−14 canisters/year). 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 prescribed medication and the dose of ICS prescribed at the index date.

Other respiratory medications and non-respiratory medications

Use of OCS (H02AB), ICS/ long-acting beta-2 agonist (LABA) (R03AK), short-acting anticholinergics (SAMA, R03BB), long-acting anticholinergics (LAMA, R03BB04), systemic beta-2 agonists (xanthines, R03), leukotriene receptor antagonists (R03DC), biological drugs, home oxygen and systemic antibiotics (J01) was recorded. Patients receiving long-term oral/systemic corticosteroid therapy (chronic regimens) were also differentiated from patients receiving iton the short-term to stabilize exacerbations/flares. The absolute and relative scheduled doses of ICS were classifiedas low, medium or high per day, according to GINA [1]. An oral/systemic corticosteroid therapy was considered short-term, 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), beta-blockers (C07), anti-inflammatory and antirheumatic drugs (M01), and antihistamines (R06A). The chronic use of OCS wasdifferentiated.

Resource use and costs

Direct healthcare costs (medical visits [primary care and specialist visits], days of hospitalization, emergency room visits, diagnostic or therapeutic procedures and pharmaceutical prescriptions) and indirect non-healthcare costs (productivity loss – days of work lost) were collected. Costs were expressed as the mean cost per patient (mean/patient) over the study period. Unit costs considered in this study are detailed in

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Supplementary Table S1. Medication cost and days of work lost cost by each patient, as well as unit costs associated with non-pharmacologic resource use, i.e. visits, and inpatient stays, etc., 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 (VAT) 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 inter-professional salary (source: *Instituto Nacional de Estadística*, INE) [26].

Statistical methods

A descriptive univariate statistical analysis was performed. Qualitative data were described using absolute and relative frequencies, and quantitative data using the mean and standard deviation (SD). The 95% confidence intervals (CI) of estimated parameters were based on the total number of subjects with non-missing values. In the bivariate analysis, the ANOVA, chi-square tests and correlation (Spearman) 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 healthcare costs (dependent variable) adjusted for covariates. The covariates included were sex, age, time since diagnosis, general comorbidity (Charlson index), which was considered as an ordinal variable with incremental values from 0 to 37, asthma severity (GINA)[1], which was considered as an ordinal variable with incremental values from 1 to 5, and previous exacerbations.

AnANCOVAmodel (procedure: marginal means, Bonferroni adjusted) was used to determine the relationship between asthma severity (GINA) [1] (independent variable) and healthcare 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.

Due to the large sample size (nearly 40,000 patients), and in order to facilitate interpretation of results (avoiding transformation of variables, etc.), non-parametric methods (Central Limit Theorem approach) were used. This approach is asymptotically valid as sample sizes increase [27], with the Central Limit Theorem-based methods providing at least as accurate an estimate ofstandard errors as, for example, the bootstrap[28].Statistical significance was set at$p< 0.05$. The analysis was conducted using SPSS for Windows version 23.

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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, 39,555 patients who met the selection criteria were analyzed and followed during the study period (**Figure 1**). The mean age of patients was 49.8 years, 64.2% were female, and the mean (SD) Charlson index was 0.7 (1.0) (**Table 1**).During the 12-month follow-up, concomitant medication was prescribed to 70.1% of all patients (**Table 2**). Nonsteroidal anti-inflammatory drugs (35.8%) and antihistamines (35.0%) were the most commonly prescribed drugs.Overall, asthma-related medication included OCS for chronic use (> 6 months) prescribed in 5.1% of patients and leukotriene receptor antagonists and home oxygen therapy prescribed in 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 ($p < 0.001$, **Table 3**). Most comorbidities increased according to GINA classification step. SABA overuse (≥ 3 prescribed canisters/year) occurred in 28.7% (95% CI: 27.7% – 29.7%) of patients, with a mean (SD) of 3.3 (3.6) canisters/year. According to the GINA classification, these percentages were 25.4%, 17.3%, 26.4%, 33.4% and 48.7% ($p < 0.001$), respectively. Overall, 5.1% of patients were prescribed ≥ 12 canisters/year.

ICS were underusedin 13.4% of patients (**Table 3**). According to the GINA classification, these percentages were 17.1%, 15.8%, 9.9%, and 7.0% ($p< 0.001$), respectively (starting from step 2). Furthermore, while ICS recommended use increased across GINA steps, underusedecreased across GINA steps. The percentage of patients with at least one exacerbation was 45.0% (according to GINA, from steps 1 to 5: 39.7%, 34.5%, 44.3%, 49.5% and 59.8%, respectively; $p < 0.001$). 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, $p< 0.001$).

Gross and adjusted resource use and costs during the follow-up by GEMA steps are described in **Table 4**. Overall numbers for annual mean (SD) primary care visits were 9.3 (10.8), specialist visits 1.5 (1.8), hospital emergencies 0.8 (1.1) and days of hospitalization 2.9 (4.1). 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, $p< 0.001$).

Of the total costs generated by asthma patients included in the study, 87% corresponded to direct healthcare costs and 13% to indirect costs (productivity loss), with a total annual mean (SD) cost of €3,001 (€3,312) per patient(€3,312) (**Table 4**). The major cost drivers were inpatient stays (40.6%), associated medication (23.9%), productivity loss (13%), and primary care visits (7.2%).Total costs increased according to GINA severity;with the mean annual cost perpatient with asthma adjusted for covariates (ANCOVA) being €2,231, €2,345, €2,735, €3,473, and €4,243, respectively ($p < 0.001$).

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Between-step differences were maintained for direct healthcare costs. Indirect costs (productivity loss), although high, showed no significant differences.

In the binary Spearman's ordinal correlation model, SABA overuse correlated with exacerbations ($\rho = 0.792$; $p< 0.001$) and healthcare costs ($\rho = 0.621$; $p< 0.001$); and exacerbations correlated with the total cost ($\rho = 0.809$; $p< 0.001$).In the adjusted multiple linear regression model, SABA overuse was associated with higher healthcare costs ($\beta = 0.479$; $p < 0.001$).

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

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

In summary, patients with SABA overuse presented with a significant increase in the mean number of exacerbations during the 1-year follow-up (1.9 *vs*. 0.2; $p < 0.001$), higher mortality rates (2.5% *vs*. 0.8%; $p < 0.001$) and increased healthcare costs (€5,702 *vs*. €1,917; $p < 0.001$).Additionally, the underuse of ICS, compared with recommended use, was associated with a higherexacerbation rate (1.2 *vs*. 0.6; $p < 0.001$ unadjusted model) and an increase in healthcare costs (€4,116 *vs*. €2,902; $p < 0.001$ unadjusted model).

Discussion

The goals of asthma treatment are to achieve symptom control and minimize the risk of exacerbations, with treatment with ICS as the cornerstone of asthma management in order to control airway inflammation [1]. However, our results confirm notable overuse of SABA in asthma patients in Spain, with almost one third of patients being prescribed more ≥3 cannister a year. Notably, 5.1% of the patients was prescribed ≥12 cannisters a year.These results suggest that SABA overuse is associated with increased healthcare resource use and costs.In the same way,underuse of ICS also generates higher costs. Total costs increased with GINA severity step. The mean total cost per patient was € 3,001. The major cost drivers were hospital admissions (40.6%), associated medication (23.9%), and productivity loss (13%). While total and direct costs were significantly higher according to increasing GINA steps, productivity loss did not show significant differences between steps.

Welsh and Cates (2010) estimated that nearly one-third of adult patients with asthma overused SABA and5.1% of patients were prescribed an excessive number of SABA canisters (≥12 canisters/year) [29]. Similar results were reported for children [21, 30]. Importantly, the frequent use of SABA has been identified as a key indicator of poor asthma control [31], and the use of 3 or more inhalers/year in asthma has been associated with a two-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, the inappropriate use of SABA remains problematic in a significant

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percentage of patients with asthma, andis associated with increased use of medical care and a higher risk of adverse outcomes. The excessive use of SABA and the fluctuating character of asthma may be due, in part, to the fact that patients are often unaware of the lack of control of their disease, despite presenting with symptoms and exacerbations. SABA used asneeded for symptom relief, together with the natural tendency of patients to seek immediate symptom relief, may contribute to more attention being paid to symptom management rather than treating the underlying inflammation inherent in asthma, which could result in over-reliance on SABAs [33, 34]. According to the results, SABA use may need to be restricted or combined with an alternative treatment in patients with confirmed asthma diagnosis, although additional data are needed to have an impact on routine clinical practice.In this sense, the GINA recommends as-needed fixed ICS/formoterol combination on demand as the preferred reliever therapy in all asthma steps [1]. Accumulated data of trials and real-world studies confirmed the higher efficacy of ICS/formoterol on demand in prevention of asthma exacerbations compared with reliever therapy with SABA as-needed [35]. All these data together with the lack of anti-inflammatory actions of SABA as initial treatment in mild asthma, and the increased risk of exacerbations associated to SABA overuse, place ICS/formoterol combination in an advantageous therapeutic position in comparison to SABA monotherapy-associated overuse, adverse effects, and costs. Nevertheless, physician-patient shared decision-making should consider not only the available pharmacological repertoire but also other clinical and non-clinical features as patient's characteristics, needs, goals and preferences, asthma activity and control, inhalation technique education, comorbidities, modifiable risk factors, environment control, or patient's adherence to treatment [36].

Patients with SABA overuse had more annual exacerbations and higher annual healthcare costs than those with recommended use. Indeed, some studies have shown that SABA overuse is a risk factor for exacerbations [37], mortality [38], and healthcare 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 highest costs were associated with hospitalizations, medications, and medical visits. Furthermore, healthcare 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 SABINAprogram [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 (hospitalization, emergency visits) of asthma is attributable to poor asthma control.Therefore, strategies aimed at generating cost savings should include greater use of preventive medication, especially inhaled steroids, and ensuring an improved patienteducation [1, 11, 42].

This study is subject tosome limitations asasthma categorization and a possible bias in patient classification, the selection of the therapeutic groups, and cost measures, which

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are attributable to the information system. Besides, other limitations are inherent to the observational retrospective nature of our study such as disease underreporting (i.e. not all asthma patients would have been identified), differences in disease management among healthcare professionals, possible inaccuracy of diagnostic coding and other comorbidities, and the lack of some variables that could influence results (socioeconomic level, work exposure, etc.). Possible confounding variables affected the study variables equally. Potential sources of bias include the classification of patients by GINA severity according to prescribed medication (although this possible inaccuracy might affect all groups in a similar way) and the percentage of medicated patients not recorded in the database (private hospitals outside the public health system, private purchase of medicine, etc.) and therefore not included. However, most patients, even those treated in private care, obtained prescriptions from the public health system to reducecosts. In addition, we could not ensure that canisters collected from the pharmacy were actually taken, as it is common that patients collect several SABA canisters for potential use in different everyday scenarios (e.g. at home, in the car, at work, etc.), which does not mean actual overuse. Last, direct non-healthcare costs (those considered "out-of-pocket costs" or 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. It should be noted that, without adequate standardization of the methodologies used, the results of this study and their external validity should be interpreted with caution.

The aim of this study is the promotion ofappropriate treatmentmanagement that can be replicated in other health institutions,to improve the quality of life of people with asthma and their capacity to perform all daily living activities.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, and highlights the relationship between SABA overuse, increased resource use, and higher direct and indirect healthcare costs due to productivity loss.

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Conflict of interest

A. Valero has received honoraria for speaking engagements at sponsored meetings from 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

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V. Plaza has received honoraria for speaking engagements at sponsored meetings from AstraZeneca, Boehringer-Ingelheim, MSD and Chiesi in the last three 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 AstraZeneca, Chiesi and Menarini.

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

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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 2020;21:0.doi: 10.18176/jiaci.0630.
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. Journal of Allergy and Clinical Immunology 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. Canadian family physician Medecin de famille canadien 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.
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.
34. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? Eur Respir J 2017;50.
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.
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;91:9 de marzo: e1-e15.
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.

Figures and Tables

Figure 1. Study flow chart. **GINA**, Global Initiative for Asthma.

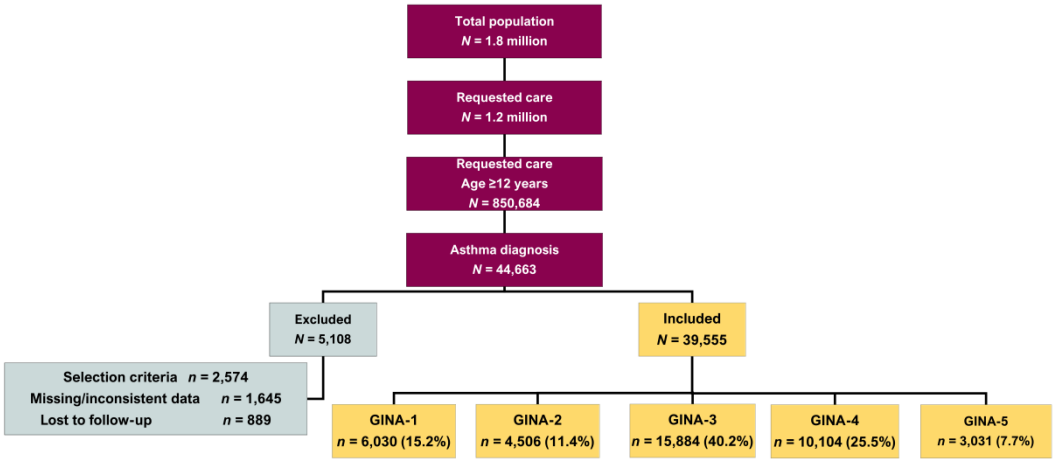

Figure 2. Total costs (EUR) per patient over the study period (one year) according to overuse and recommended use of SABA (**A**), underuse and recommended use of ICS (**B**), and exacerbations (**C**). GINA, Global Initiative for Asthma; **ICS**, Inhaled corticosteroids; **SABA**, Short-acting beta-2 agonists; EUR, Euro.

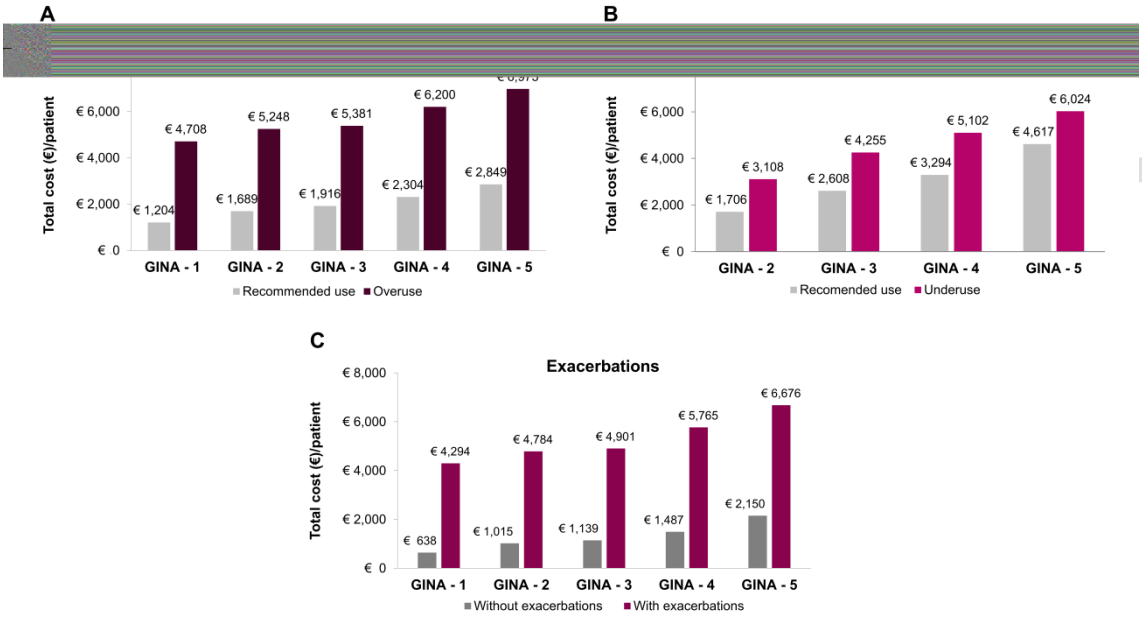

Table 1. Baseline characteristics of patients.

Demographic characteristics	***N* = 39,555**
Age (years), mean (SD)	49.8 (20.7)
Sex (female), (%)	64.2
Other variables, mean (SD)	
Time since diagnosis (years)	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 index score	0.7 (1.0)
Associated comorbidities, %	
Hypertension	28.4
Diabetes mellitus	11.1
Dyslipidemia	31.0
Obesity	27.7
Active smokers	11.2
Ischemic heart disease	4.2
Cerebrovascular accident	3.0
Heart failure	4.3
Renal failure	2.5
COPD	9.7
Atopic dermatitis	34.5
Allergic rhinitis	55.7
Chronic rhinosinusitis with nasal polyps	11.0

BMI, body mass index; **COPD**, chronic obstructive pulmonary disease; **FEV_1**, forced expiratory volume in the first second; **SD**, standard deviation.

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, chronic use (>6 months)	5.1
Systemic antibiotics	14.8
Inhaled corticosteroids	11.4
ICS/LABA	73.4
Short-acting anticholinergics	4.7
Systemic beta-2 agonists (xanthines)	3.2
Leukotriene receptor antagonists	27.1
Biological drugs	0.3
Home oxygen therapy	2.9
Groups of concomitant medication, %	
Acetylsalicylic acid	6.6
Proton-pump inhibitor	30.5
Beta-blockers	7.1
Non-steroidal anti-inflammatory drugs	35.8
Antihistamines	35.0
Mean concomitant medication, mean (SD)	1.1 (1.0)
Use of concomitant medication, %	
0	29.9
1	37.4
2	22.4
≥ 3	10.3

ICS, inhaled corticosteroid;**LABA**, long-acting beta-2 agonist; **SD**, standard deviation

Table 3. SABA overuse (defined as ≥ 3 canisters/year), ICS use, and description of exacerbations and mortality during the follow-up period by study groups.

Study groups	GINA–1	GINA–2	GINA–3	GINA–4	GINA–5	Total	*p*-value
Patients, *n* (%)	6,030 (15.2)	4,506 (11.4)	15,884 (40.2)	10,104 (25.5)	3,031 (7.7)	39,555 (100)	<0.001
Use of SABA							
Canisters/year, mean (SD)	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/year, %	25.4	17.3	26.4	33.4	48.7	28.7	<0.001
SABA ≥ 12 canisters/year, %	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	<0.001
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 year), %	50.4	45.8	52.8	56.3	64.1	53.5	
Follow-up period (1 year)							
Patients with exacerbations, %	39.7	34.5	44.3	49.5	59.8	45.0	<0.001
Exacerbations, mean (SD)	0.6 (0.9)	0.5 (0.8)	0.7 (0.9)	0.8 (1)	1.1 (1.1)	0.7 (0.9)	
Nº of 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	<0.001

GINA, Global Initiative for Asthma; **ICS**, **i**nhaled corticosteroids; **SABA**, short-acting beta-2 agonists, **SD**, standard deviation.

Table 4. Resource use and direct healthcare costs and indirect costs during follow-up (one year): raw and adjusted costs by GINA step.

GINA Step	GINA–1	GINA–2	GINA–3	GINA–4	GINA–5	Total
Patients, *n* (%)	6,030 (15.2)	4,506 (11.4)	15,884 (40.2)	10,104 (25.5)	3,031 (7.7)	39,555 (100)
Resources use						
Medical visit						
Primary care (nº of visits), mean (SD)	7.9 (9.5)	9.2 (10.5)	8.7 (10.1)	10.2 (11.6)	12.3 (13.1)	9.3 (10.8)
Specialist care (nº of visits), mean (SD)	1.2 (1.7)	1.1 (1.6)	1.4 (1.6)	1.7 (2.0)	2.4 (2.4)	1.5 (1.8)
Emergency room (nº of visits), mean (SD)	0.7 (1.0)	0.6 (1.0)	0.8 (1.1)	0.9 (1.1)	1.2 (1.3)	0.8 (1.1)
Hospital stay (days), mean (SD)	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
Supplementary tests (nº), mean (SD)						
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)
Lost productivity (days), mean (SD)	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						
Primary care (nº of visits), mean (SD)	182 (220)	214 (244)	202 (235)	237 (270)	286 (303)	216 (250)
Specialist care (nº of visits), mean (SD)	111 (158)	103 (148)	125 (151)	157 (184)	223 (220)	136 (170)
Emergency room (nº of visits), mean (SD)	82 (117)	70 (116)	92 (130)	105 (132)	140 (158)	95 (130)
Hospital stay (in days), mean (SD)	995 (1,513)	903 (1,508)	1,137 (1,595)	1,442 (1,901)	1,820 (2,072)	1,219 (1,716)
Supplementary tests, (nº), mean (SD)						

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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)
CAT	2 (16)	2 (24)	2 (17)	4 (31)	9 (47)	3 (25)
NMR	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)
Pharmaceutical prescriptions, mean (SD)						
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)
Health costs (€), mean (SD)	1,718 (2,020)	1,910 (2,032)	2,424 (2,155)	3,202 (2,579)	4,456 (2,993)	2,612 (2,425)
Indirect costs (productivity loss) (€), mean (SD)	371 (1,745)	407 (2,097)	380 (1,986)	403 (1,977)	400 (2,477)	389 (2,005)
Total costs (€), mean (SD)	2,088 (2,871)	2,317 (3,090)	2,805 (3,093)	3,605 (3,422)	4,856 (4,021)	3,001 (3,312)
Adjusted costs per patient (€) (ANCOVA)*, mean (95% CI)						
Direct healthcare costs	1,898 (1,841-1,955)	1,981 (1,914-2,047)	2,368 (2,332-2,404)	3,079 (3,034 – 3,125)	3,837 (3,751-3,922)	
Indirect costs (productivity loss)	333 (280-385)	364 (303-424)	366 (333-399)	394 (352-435)	406 (328-485)	
Total costs	2,231 (2,149-2,312)	2,345 (2,249-2,440)	2,735 (2,683-2,786)	3,473 (3,408-3,538)	4,243 (4,120-4,366)	

CAT, computed axial tomography; **CI**, confidence interval; **GINA**, Global Initiative for Asthma; **NMR**, nuclear magnetic resonance;**SD**, standard deviation

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