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Healthcare costs and resources utilization in children with difficult-to-control asthma treated with biologic therapies: A population-based cohort study

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Abstract

Introduction: Asthma is one of the most common diseases in children, with a variable range of severity. In recent years, treatment for severe asthma has been largely improved by the availability of targeted biologic therapies. Nevertheless, studies reporting real-world data and cost-effectiveness analyses are lacking. The aim of this study was to evaluate, on a population-based cohort of children with asthma, the impact of the treatment with biologics on healthcare service utilization and associated costs.

Methods: Data were retrieved from Healthcare Utilization database of Lombardy region (Italy). A cohort of 46 asthmatic children aged 6–11 in treatment with dupilumab, mepolizumab or omalizumab was identified during 2017–2021. We compared healthcare resources use between the year before ("baseline period") and the year after the treatment initiation ("follow-up period"). Average 1-year healthcare costs were also calculated.

Results: Comparing the *baseline* with the *follow-up* period, the number of patients with at least one exacerbation-related hospitalization and ER access decreased by 75.0% and 85.7%, respectively. The use of biologic agents, namely omalizumab, mepolizumab and dupilumab, significantly reduced oral corticosteroids (OCS), short-acting β2-agonists and the association inhaled corticosteroids/long-acting β2-agonists use. ER admissions for non-respiratory causes were also significantly reduced, while discontinuation rate was low (6.5%). The overall costs increased, due to the costs of the biologic agents, but the hospital admission-related costs due to respiratory causes reduced significantly.

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification System; ER, emergency-room; FeNO, fractional exhaled nitric oxide; GINA, global initiative for asthma; HCU, healthcare utilization databases; ICD, International Classification of Diseases; ICS, inhaled corticosteroids; LABA, long-acting βeta-agonists; NHS, National Health Service; OCS, oral corticosteroids; RCT, randomized controlled trials; RHS, regional health service; SABA, short-acting beta-agonists; SAS, statistical analysis system software; SD, standard deviation.

Conclusions: Our real-world investigation suggests that biologic agents reduced hospital admissions for respiratory causes and use of anti-asthmatic drugs, including OCS. However, long-term healthcare sustainability still needs more in-depth assessments.

KEYWORDS
children, dupilumab, mepolizumab, omalizumab, severe asthma

1 | INTRODUCTION

Asthma is one of the most common diseases in children, with a variable range of severity that consistently impacts on the healthcare system with an increasing burden.[1] In fact, asthma is often associated with recurrent exacerbations and persistent symptoms, thus the costs associated with asthma management increase as disease control worsens.[2]

In the last decade, treatment for severe asthma has been largely improved by the availability of new targeted biologic therapies, modulating specific cell signaling pathways. Three of these biologic agents (omalizumab, mepolizumab, and dupilumab) have been recently approved for children aged 6–11 years.[3] In particular, in Italy, for 6–11 years old children, omalizumab was approved since 2014, mepolizumab since September 2020 and dupilumab since April 2022.[4,5]

Randomized controlled trials (RCT) in children and adolescents have been shown to reduce the rate of asthma exacerbations and to improve lung function, oral corticosteroid (OCS) use and quality of life.[6,7] Nevertheless, only a limited number of studies reported real-world data and cost-effectiveness analyses, showing a reduction of the annual rate of severe asthma exacerbations by at least 40%–50% (some up to 70%), and a reduction of 89% for hospitalizations (after 1 year of treatment with omalizumab).[8,9] Significant improvements in lung function and asthma control were observed with omalizumab and a corticosteroid sparing effect also has been demonstrated after treatment with mepolizumab and omalizumab.[9–11] Furthermore, these therapies have reassuring safety profiles in pediatric patients, and have the potential to become cost-effective, especially in patients with recurrent exacerbations.[12]

The aim of this study was to evaluate, on a population-based cohort of pediatric patients with asthma, the impact of the treatment with biologics (i.e., dupilumab, mepolizumab, and omalizumab) on healthcare service utilization and associated costs. More specifically, we evaluated (i) the use of anti-asthmatic drugs other than biologics, including OCS, and (ii) the rates of hospital admissions, both ordinary hospitalizations and emergency room (ER) visits, related to either asthma exacerbations or non-respiratory causes. Healthcare costs and the discontinuation rate of biologics were also evaluated.

2 | MATERIALS AND METHODS

2.1 | Setting and data source

The study was based on the computerized Healthcare utilization (HCU) databases of Lombardy, a region of north-western Italy which accounts for almost 10 million residents (about 16% of the whole national population). In Italy all citizens have equal access to healthcare provided by the National health service (NHS) and, in Lombardy as in other regions, an automated system of HCU databases is used to manage health services. HCU databases collects a variety of information on the beneficiaries of the regional health service (virtually all the residents in the region), such as socio-demographics, diagnoses at discharge from public or private hospitals, specialist visits, diagnostic examinations, ER admissions and drug prescriptions dispensed in outpatient and inpatient settings by the NHS.[13,14] These various types of data can be interconnected since a unique personal identification code is used by all databases for each NHS beneficiary. To preserve privacy, each identification code is automatically anonymized (with the inverse process being only allowed to the Regional Authority upon special request of judicial Authorities).

Further details on HCU databases in the field of respiratory diseases have been reported elsewhere.[15–18] The codes of drug therapies and diagnostic procedures used in the current study for drawing records and fields from the aforementioned databases are reported in Table S1.

2.2 | Cohort selection

The target population consisted of all the children aged 6–11 years residents in Lombardy (about 540,000 inhabitants in 2023) and beneficiaries of the regional health service (RHS). Of these, patients who received at least one prescription of omalizumab, mepolizumab or dupilumab, between January 2017 and December 2021, were identified. The date of their first administration during the recruitment period was recorded as index date.

The inclusion and exclusion criteria for the cohort selection are summarized in Figure 1. Patients were excluded whether they, during the year before the index date: (i) were beneficiaries of the RHS from

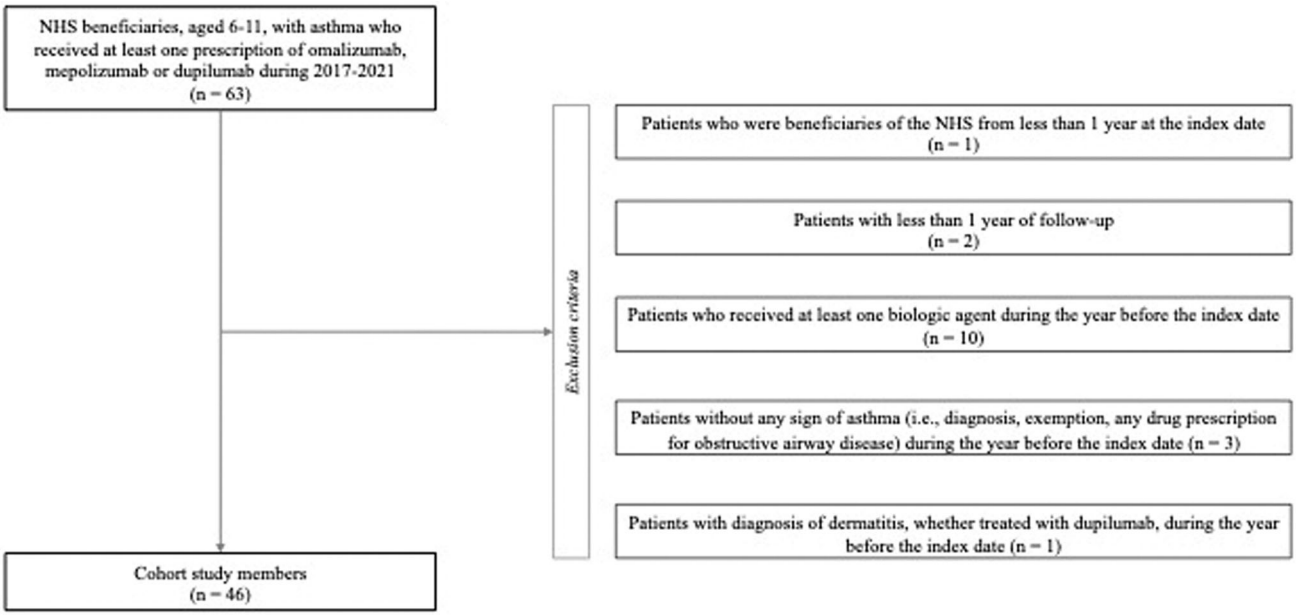

FIGURE 1 Flow-chart of inclusion and exclusion criteria for the eligibility of children with a diagnosis of asthma and receiving at least one prescription of a biologic agent during the period 2017–2021. Lombardy, Italy, 2016–2022.

less than 1 year; (ii) received at least one prescription of another one of the considered biologic agents; (iii) did not experience any sign of asthma (please see below); (iv) received a diagnosis or a drug prescription for dermatitis (only for patients treated with dupilumab). Patients who (v) experienced less than 1 year of follow-up were also excluded, and the remaining patients constituted the study cohort.

Patients were defined as having asthma if they met at least one of the following criteria: (i) diagnosis of asthma as per ICD-9-CM codes; (ii) asthma exemption; or (iii) any prescription of drug for obstructive airway disease, including inhalation therapy with bronchodilators and inhaled corticosteroids (ICS). Further details on chronic respiratory diseases and drug therapies considered in the cohort selection are reported in Table S1.

Although we excluded children receiving dupilumab with a diagnosis of atopic dermatitis, this disease is not covered by a specific exemption in Italy and is less likely to cause hospital admissions; therefore we cannot exclude that some asthmatic children receiving dupilumab in our cohort also had atopic dermatitis as comorbidity.

2.3 | Study design and outcomes

For each child included in the study cohort, starting from the index date, two periods of observation were considered and compared to each other: the "*baseline period*," defined as the period of 1 year immediately preceding the index date, and the "*follow-up period*," defined as the year immediately following the index date. In both periods, all the medications, hospital admissions, ER accesses and outpatient visits were recorded.

The exposure was the treatment with omalizumab, mepolizumab, or dupilumab, whereas the main outcome of interest was the use of anti-asthmatic drugs other than biologics, during the follow-up period compared to the use during the baseline period. The use of anti-asthmatic drugs was assessed with several measures. The two main measures evaluated were the changes comparing the follow-up period to the baseline period in (i) the percentage of patients with at least one prescription of the considered drugs, and (ii) the mean number of drug prescriptions per patient. These changes were measured for: OCS, ICS, montelukast, antihistamines, short-acting beta agonists (SABA), ICS + long-acting beta agonists (LABA), azithromycin, and amoxicillin with beta-lactamase inhibitors.

The changes comparing the follow-up period to the baseline period were also evaluated for the rates of hospital admissions, both ordinary hospitalizations and ER accesses, related to either asthma exacerbations or non-respiratory causes.

Furthermore, as secondary outcomes, we evaluated treatment discontinuation of biologics at 6 months after treatment initiation, and the healthcare costs.

Prescriptions of biologics were considered "consecutive" if the interval between the end of one prescription and the start of the following one was less than 180 days, and "interrupted" otherwise; interrupted prescriptions were considered to lead to discontinuation of treatment.

Concerning the other secondary outcome of our study, healthcare costs were assessed from the amount that the regional health authority reimbursed to health providers for healthcare services. Costs included hospital admissions, ER accesses, outpatient services and drugs dispensed by the NHS, and were assessed separately for all the respiratory related and non-respiratory related healthcare services provided, respectively. With the aim of expressing cost as a rate, healthcare costs accumulated overall by the cohort were divided by the number of person-years accumulated. The average

1-year healthcare costs were calculated and expressed in Euros every person-year. The change of this measure between the baseline and the follow-up period was estimated.

2.4 | Statistical analysis

Continuous variables were described as mean, standard deviation (*SD*) and/or median, whereas absolute frequencies and related percentages were reported for categorical variables. The comparisons of outcome measures between the baseline and the follow-up period were performed using (i) the Student *t* test for the means of paired samples for continuous variables, and (ii) the χ^2 test for categorical variables.

All analyses were performed using the software SAS (version 9.4 for Windows; SAS Institute, North Carolina, United States). Two-tailed *p* values less than .05 were considered to be significant.

3 | RESULTS

Out of the 63 children (aged 6–11 years) having asthma and with at least one prescription of a biologic agent during the period 2017–2021, 46 [58.7% males, mean (*SD*) age 9.1 (1.9) years] met all the inclusion criteria and were included in the final analysis, Figure 1. As reported in Table 1, omalizumab was the most frequently prescribed biologic agent (37 cases, 80.4%), followed by mepolizumab (5, 10.9%) and dupilumab (4, 8.7%). After the treatment initiation with a biologic agent, no patient experienced a therapy switch to another biologic. Two patients had a concomitant diagnosis of cystic fibrosis. Furthermore, one patient had mental disorders and another one suffered from epilepsy, while none presented eosinophilic granulomatosis with polyangiitis (EGPA). During the year before the initiation of the biologic agent, 38 patients (82.6%) received at least one prescription of other anti-asthmatic drugs, while one patient received antiepileptic drugs and, among the two patients with concomitant cystic fibrosis, one received prescriptions of ivacaftor/lumacaftor, a Cystic Fibrosis Transmembrane Regulator modulator (Table 1).

In regard to study outcomes, the number of patients requiring at least one prescription of OCS decreased by 45.2% in the follow-up compared to the baseline period (67% vs. 37%, $p = .0035$) and also the mean number of prescriptions in treated children significantly decreased (Table 2).

The overall number of patients receiving at least one prescription of anti-asthmatic drugs other than biologic agents, such as ICS and montelukast, over a 12-month period did not significantly change between the two study periods, as shown in Table 2. Similar findings were reported for the antihistamine class. Otherwise, in patients with at least one prescription of other respiratory drugs (ATC code R03, excluding biologic agents) the mean number of prescriptions per year decreased from 9.9 to 7.1, $p = .0033$. This suggests that the number of distinct patients assuming these therapies did not change, but it was the intensity of prescriptions to decrease. In particular, we observed a significant reduction, around 40%, in the mean number of prescriptions of SABA, reliever medications for asthma flare-ups, and ICS + LABA for treated patients (Table 2). No significant changes were observed in the prescriptions of antibiotics (azithromycin and amoxicillin with beta-lactamase inhibitor) (Table 2).

The number of patients requiring at least one exacerbation-related hospitalization decreased by 75.0% in the year after biologic treatment initiation compared to the baseline period (16 vs. 4 patients, $p = .0024$) and, among them, the number of hospitalizations showed a significant decrease (1.3 vs. 0.5, $p = .0178$) (Table 2). No differences were observed regarding hospitalizations for non-respiratory causes, which mainly included epileptic syndrome and infections, such as adenovirus infections.

Concerning ER accesses, both the admission for respiratory and non-respiratory causes show a significant decrease between the

TABLE 1 Baseline characteristics of children with asthma who received at least one dispensation of a biologic agent (dupilumab, mepolizumab, or omalizumab) during the study period (Lombardy, Italy, 2016–2022).

	Whole cohort *N* (%)
N	46
Male gender	27 (58.7)
Mean (*SD*) age (years) at index date	9.1 (1.9)
Index therapy with biologic agents	
Dupilumab	4 (78.7)
Mepolizumab	5 (10.9)
Omalizumab	37 (80.4)
Comorbidities	
Respiratory diseases other than asthma	7 (15.2)
Cystic fibrosis	2 (4.4)
Obstructive sleep apnoea syndrome	0 (0)
EGPA	0 (0)
Epilepsy	1 (2.2)
Mental disorders	1 (2.2)
Co-medications	
Other respiratory agents[a]	38 (82.6)
Antidepressants	0 (0)
Antipsychotics	0 (0)
Antiepileptics	1 (2.2)
CFTR modulators or potentiators[b]	1 (2.2)
Antineoplastics	0 (0)

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; *SD*, standard deviation.

[a]Excluding biologic agents.

[b]Among the two patients with concomitant cystic fibrosis.

TABLE 2 Use of specific healthcare services during the year preceding and the year after the start of treatment with biologic agents (Lombardy, Italy, 2016–2022).

	Baseline period	*Follow-up* period	Absolute (%) reduction	*p* value[a]
Hospital admissions				
Respiratory diseases				
Patients with at least one hospital admission	16 (34.8%)	4 (4.4%)	12 (75.0%)	0.0024[b]
Number of hospital admissions[c]	1.3 (0.6), 1	0.5 (1), 0	0.8 (61.5%)	0.0178[b]
Non-respiratory diseases				
Patients with at least one hospital admission	7 (15.2%)	9 (15.6%)	−2 (−28.6%)	0.5822
Number of hospital admissions[c]	0.8 (0.9), 1	0.8 (0.6), 1	0.0 (0%)	0.7545
Emergency-room (ER) accesses				
Respiratory diseases				
Patients with at least one ER access	21 (45.7%)	3 (6.5%)	18 (85.7%)	<0.0001[b]
Number of ER accesses[d]	1.9 (1.2), 1.5	0.2 (0.5), 0	1.7 (89.5%)	<0.0001[b]
Non-respiratory diseases				
Patients with at least one ER access	21 (45.7%)	11 (23.9%)	10 (47.6%)	0.0286[b]
Number of ER accesses[d]	1.5 (1.3), 1	0.9 (1.4), 0	0.6 (40.0%)	0.0808
Oral corticosteroids				
Patients with at least one prescription	31 (67.4%)	17 (37%)	14 (45.2%)	0.0035[b]
Number of prescriptions[e]	2.9 (1.9), 2	1.2 (1.5), 1	1.7 (58.6%)	<0.0001[b]
Other respiratory agents				
Patients with at least one prescription	38 (82.6%)	36 (72.3%)	2 (5.3%)	0.5992
Number of prescriptions[e]	9.9 (6.5), 9.5	7.1 (6.5), 6	2.8 (28.3%)	0.0033[b]
Inhaled corticosteroids				
Patients with at least one prescription	19 (41.3%)	18 (39.1%)	1 (5.3%)	0.8316
Number of prescriptions[e]	1.4 (1.4), 1	1.4 (1.6), 1	0.0 (0%)	1.0000
Montelukast				
Patients with at least one prescription	23 (50%)	20 (43.5%)	3 (13.0%)	0.5307
Number of prescriptions[e]	3.9 (2.9), 3	3.8 (3.2), 3	0.1 (2.6%)	0.7559
Antihistamines				
Patients with at least one prescription	26 (56.5%)	19 (41.3%)	7 (26.9%)	0.1443
Number of prescriptions[e]	2.6 (1.5), 2.5	3.5 (2.6), 3	−0.9 (−34.6%)	0.1715
Short-acting beta agonists				
Patients with at least one prescription	33 (71.7%)	27 (58.7%)	6 (18.2%)	0.1891
Number of prescriptions[e]	5.2 (5.8), 3.5	3.2 (5.3), 2	2.0 (38.5%)	0.0056[b]
Inhaled corticosteroids + long-acting beta-2 agonists				
Patients with at least one prescription	33 (71.7%)	26 (56.5%)	7 (21.2%)	0.1281
Number of prescriptions[e]	5.3 (3.7), 4	3.5 (3.0), 3.5	1.8 (34.0%)	0.0077[b]
Azithromycin				
Patients with at least one prescription	12 (26.1%)	8 (17.4%)	4 (33.3%)	0.3120
Number of prescriptions[e]	3.1 (3.8), 2	2.6 (1.9), 1	0.5 (16.1%)	0.1106

(Continues)

TABLE 2 (Continued)

	Baseline period	*Follow-up* period	Absolute (%) reduction	*p* value[a]
Amoxicillin and beta-lactamase inhibitor				
Patients with at least one prescription	15 (32.6%)	10 (21.7%)	5 (33.3%)	0.2413
Number of prescriptions[e]	1.3 (1.1), 1.5	0.9 (1.2), 0	0.4 (30.8%)	0.2542

[a]*p* value for the comparisons of outcome measures between baseline and follow-up period: χ^2 test for categorical variables, or the Student *t* test for the means of paired samples for continuous variables.

[b]Statistical significance at an *alpha* level of .05.

[c]On patients who experienced at least one hospital admission; reported as mean (*SD*), median.

[d]On patients who experienced at least one emergency-room access; reported as mean (*SD*), median.

[e]On patients who experienced at least one specific drug prescription; reported as mean (*SD*), median.

baseline and follow-up period. Among the non-respiratory causes of ER access, the most common before the initiation of the biologic agent were urticaria, emotional disturbances of childhood, polymyalgia rheumatica and eczema, while, after the initiation of the biologic agent, the most common cause was abdominal pain.

During the first 6 months after the treatment initiation with a biologic agent, only 3 out of 46 patients (6.5%) of our cohort did not renew the prescription.

The mean overall healthcare costs nearly doubled during the considered periods, from 6108.5€ to 15409.4€. As can be noticed from Table 3, this increase in healthcare expenditures was mainly led by the added costs of biologic treatments. Significant reductions were observed for healthcare costs related to ER accesses for respiratory diseases and for treatment with anti-asthmatic and other respiratory drugs.

4 | DISCUSSION

To the best of our knowledge this is the first population-based cohort study analyzing the impact of biologics on healthcare resources utilization in children with asthma using data retrieved by HCU databases.

Although information to completely evaluate asthma severity (e.g., symptoms and asthma control questionnaires) is not available in HCU databases, together with other clinical data, we can infer that the majority of patients in our cohort had difficult-to-treat asthma according to the Global Initiative for Asthma (GINA) 2023 guidelines.[19] Indeed, difficult-to-treat asthma is defined as asthma that is uncontrolled despite GINA Step 4 or 5 treatment (e.g., medium or high dose ICS with a second controller; maintenance OCS), or that requires such treatment to maintain good symptom control and reduce the risk of exacerbations. In our cohort 67.4% received at least 1 prescription of OCS in the baseline year (with a mean of 2.9 prescriptions per year), 71.7% received at least 1 prescription of ICS + LABA (mean of 5.3 prescriptions per year) and 71.7% received at least 1 prescription of SABA (mean of 5.8 prescriptions per year).

In this real-world study we observed that the number of patients with at least one exacerbation-related hospitalization and ER access decreased by 75.0% and 85.7%, respectively, in the year after the initiation of the treatment with a biologic agent.

Our findings are similar to those by Deschildre et al.,[9] who reported, in a real-world long-term study on 101 severe allergic asthmatic children (6–18 years) receiving omalizumab, a drop of 72% in severe exacerbation rate and of 88.5% for hospitalizations in the year receiving the biologic treatment compared to the prior one. Similarly, in an Italian 1-year real-life multicentre survey on 47 pediatric patients with severe allergic asthma, the ER evaluations and hospital admissions were reduced by 90% and 94%, respectively, in the year after the initiation of omalizumab compared to the prior one.[8]

Although RCTs are the gold standard for establishing the approval of drugs like targeted biological treatment, a significant proportion of patients in routine clinical practice do not conform to the strict inclusion criteria, so there might be discrepancies between RCTs efficacy and real-world effectiveness. Our study population included two patients affected by cystic fibrosis, one by epilepsy and one by mental disorders: these patients would have probably been excluded from these trials. Therefore, real-world research is necessary to confirm efficacy and safety of biologics also in patients with multiple or rare comorbidities.

Most real-world data available for biologicals utilization in severe pediatric asthma regard omalizumab, which was the first biologic drug approved for children worldwide and in Italy since 2014.[4] Our study confirms this prevalence and omalizumab is by far the most prescribed targeted biologic treatment in our cohort (80% of cases). Furthermore, for the purpose of this study, we included in the analysis all the children with a diagnosis of asthma receiving biologics although, up to the end of the cohort selection period, the only indication for the prescription of dupilumab in children aged 6–11 years in Italy is severe atopic dermatitis. Therefore, the four patients receiving dupilumab were likely suffering for both asthma and atopic dermatitis.

The efficacy of some biologic drugs on the dermatological manifestations of allergic diseases is well known.[20,21] In fact, not only dupilumab is approved for the treatment of severe atopic dermatitis, but also omalizumab for the treatment of severe urticaria.[20,21]

Interestingly, although our study was not designed for this purpose, in the year after the biological drug introduction we

TABLE 3 Mean (standard deviation) healthcare costs in Euros (€) covered by NHS per person-year in the baseline and follow-up period, respectively (Lombardy, Italy, 2016-2022).

	Baseline period	*Follow-up* period	*p* value[a]
Hospital admissions	1584.3 (2437.3)	954.7 (3034.5)	.0920
Respiratory diseases	1173.2 (1953.8)	431.9 (2030.8)	.0537
Non-respiratory diseases	411.1 (1471.3)	522.7 (1919.1)	.3985
ER accesses	97.3 (104.5)	39.9 (101.5)	.0054[b]
Respiratory diseases	55.0 (79.2)	4.7 (20.3)	.0001[b]
Non-respiratory diseases	42.3 (66.2)	35.2 (88.2)	.6586
Drugs	3714.2 (20674.5)	13597.4 (22752.4)	<.0001[b]
Biologic agents	0	9,704.7 (5798.6)	<.0001[b]
Dupilumab	0	797.5 (2886.3)	.0674
Mepolizumab	0	1050.4 (3109.3)	.0267[b]
Omalizumab	0	7856.8 (6857.2)	<.0001[b]
Specific anti-asthmatic drugs[c]	273.1 (225.5)	196.8 (168.7)	.0062[b]
Other respiratory agents[d]	249.1 (221.1)	177. 6 (163.1)	.0064[b]
Non-respiratory drugs[e]	3192.0 (20670.4)	3518.3 (22621.7)	.2757
Outpatient services	712.7 (785.5)	817.4 (807.9)	.3647
Respiratory	1.6 (10.5)	0	.3227
Non respiratory	711.1 (785.4)	817.4 (807.9)	.3572
Total	6108.5 (21845.3)	15409.4 (25027.3)	<.0001[b]

Abbreviations: ER, emergency-room; NHS, national health service.

[a]*p* value for the comparisons of outcome measures between baseline and follow-up period: the Student *t* test for the means of paired samples for continuous variables.

[b]Statistical significance at an *alpha* level of .05.

[c]Any anti-asthmatic drug other than biologics: beta-2 agonists, inhaled corticosteroids, antimuscarinic agents, anti-leukotrienes, antihistamines; theophylline, aminophylline, glucocorticoids.

[d]Any respiratory drug excluding biologic agents and specific anti-asthmatic drugs.

[e]Any drug excluding respiratory agents (anti-asthmatic and other respiratory agents).

observed a significant reduction in ER admissions not only for respiratory causes, but also for non-respiratory causes, particularly dermatological diseases, such as eczema and urticaria. We speculate that the reduction of the dermatological causes of admission might be partially due to the biologic agents.

Our study is the first to show in a real-world setting that in a cohort of children with asthma biologics introduction also improves the control of other comorbidities, particularly those with an allergic substrate, as shown by the reduction in the ER accesses.

In regard to concomitant medications, our study confirms a significant reduction in the prescription of OCS already observed in other studies on omalizumab in children with asthma.[8,9] More controversial is the impact of biologic agents on maintenance therapy. We did not observe a reduction in the number of children with at least one prescription of respiratory medications other than OCS, but we found a significant reduction in the mean number of prescriptions of respiratory medications. This reduction was driven by SABA, which suggests a better asthma control after biologics introduction, and ICS/LABA association, while ICS alone, montelukast and antihistamines prescriptions, the milestones of maintenance therapy for pediatric asthma, did not change. A recent study based on insurance claim databases from United States and analyzing asthma medication use in the 12 months preceding and following mepolizumab initiation in children and adolescents showed no significant change in asthma treatments dispensed, including both ICS, ICS/LABA and SABA.[22] On the contrary, two real-world observational studies on the use of omalizumab in Italy and France showed a significant sparing effect on the daily ICS dose that decreased by 36% and 30%, respectively.[8,9]

We observed a discontinuation rate with biologics of 6.5%, comparable to that found in cohorts of adult patients with severe asthma from the same setting (Lombardy, Italy): 2.7% for mepolizumab and 8% for dupilumab.[16,17]

This discontinuation rate is also similar to the one reported in a French study involving omalizumab (5.8%),[9] but much lower compared to that calculated using insurance claim databases in

United States, where the discontinuation rate of mepolizumab in children and adolescents within the first 365 days of utilization was 36%.[22]

Finally, when considering healthcare costs, severe asthma and difficult-to-treat asthma have been associated with significantly higher costs compared to better controlled asthma both in children and adults.[23,24] In our cohort the cost of the biologic treatments has nearly doubled the healthcare expenditures. Similar results were observed in cohorts of adult patients with severe asthma from the same Italian region (tenfold and fourfold direct costs increase after dupilumab and anti-IL-5 introduction, respectively) and from children from the French national health insurance, in whom 65% of direct healthcare costs were attributed to medications, particularly biologics.[15,16,25] These observations suggest the need for a personalized use of biological drugs to maintain the sustainability of healthcare systems.

Our investigation, despite being based on HCU databases that provide highly accurate data in a very large and unselected population, also has some limitations beyond those inherent the observational studies. A main limitation is that, due to privacy regulations, hospital records were not available for scrutiny, which means that the diagnostic validity of asthma could not be checked. Moreover, in case of treatment discontinuation, the information on the specific cause, either inefficacy or adverse events, was not available. Another limitation of our study is related to the fact that data on main comorbid conditions were not available. Indeed, as with any observational study based on HCU databases, our study has the limitation of the lack of clinical data, such as blood exams, dosages of anti-asthmatic drugs, pulmonary function tests and asthma control questionnaires. Most of them are well-known modifiers of treatment outcome and patients' adherence and are necessary to correctly evaluate asthma severity. Finally, the small number of patients with a prescription of mepolizumab and dupilumab did not allow to perform separate analyses for each biologic agent.

These limitations notwithstanding, our findings suggest that biologic drugs, namely omalizumab, mepolizumab and dupilumab, markedly reduces OCS use and exacerbation-related hospital and ER admissions in children with asthma, without affecting adherence to maintenance therapy (mainly ICS). ER admissions for non-respiratory causes, particularly dermatological symptoms and diseases, such as urticaria and eczema, are also significantly reduced after biologics initiation, while discontinuation rate at 6 months was low (6.5%) and comparable to those observed in cohorts of adult patients with severe asthma. The overall healthcare costs doubled, mainly due to the costs of the biologic agents, but the hospital admission-related costs due to respiratory causes significantly reduced.

AUTHOR CONTRIBUTIONS

Paola Faverio and Giovanni Corrao: are the guarantors of this research. **Paola Faverio, Claudia Conflitti, Matteo Monzio Compagnoni, and Giulia Bonaiti**: were responsible for study concept and design. **Claudia Conflitti, Matteo Monzio Compagnoni, Matteo Franchi, and Giovanni Corrao**: contributed to data acquisition. **Claudia Conflitti, Matteo Monzio Compagnoni, Matteo Franchi, and Paola Faverio**: performed data analysis. **Paola Faverio, Claudia Conflitti, Matteo Monzio Compagnoni, Matteo Franchi, Veronica Capuano, Giulia Bonaiti, Chiara Vimercati, Andrea Biondi, Fabrizio Luppi, and Giovanni Corrao**: contributed to the drafting of this manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENTS

GC received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry for University and Research (MIUR). He took part to a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN, and BMS). He also received honoraria as member of Advisory Board from Roche. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All methods were carried out in accordance with the Declaration of Helsinki. According to the rules from the Italian Medicines Agency (available at: http://www.agenziafarmaco.gov.it/sites/default/files/det_20marzo2008.pdf), retrospective studies using administrative databases do not require Ethics Committee protocol approval. Furthermore, according to General Authorization for the Processing of Personal Data for Scientific Research Purposes issued by the Italian Privacy Authority on August 10, 2018 (available at: https://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/9124510) this study was exempt from patients informed consent. To protect privacy and to guarantee individual records anonymity, after the record-linkage between HCU databases and the data extraction procedure, the individual identification codes and other personal information were automatically converted into anonymous by the regional IT technicians. Thus, researchers had access to full anonymized data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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