

The Burden of Severe Asthma in France: A Case-Control Study Using a Medical Claims Database



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What is already known about this topic? Some asthma patients need high dose and continuous medications to relieve their symptoms. This form of asthma is called severe asthma according to the definition of Global Initiative for Asthma 2017.

What does this article add to our knowledge? Our work quantifies the prevalence of severe asthma in France and reports its burden in terms of comorbidities and mortality. We describe the management of severe asthma. Mean oral corticosteroid (OCS) consumption in this population is above 3 boxes/patient/year.

How does this study impact current management guidelines? The burden of severe asthma and the extremely high OCS use in this population may indicate poor overall control of severe asthma and the need for a clearer care pathway.

BACKGROUND: Severe asthma (SA) is defined by treatment intensity. The availability of national databases allows accurate estimation of the prevalence, long-term outcomes, and costs of SA.

OBJECTIVE: To provide accurate information on SA, focusing on comorbidities, mortality, health care resource consumption, and associated costs.

METHODS: A cohort of patients with SA identified in 2012 was extracted from a French representative claims database and followed for 3 years. Their characteristics, comorbidities,

mortality, and direct costs were compared with a matched control group without asthma.

RESULTS: A total of 690 patients with SA were matched to 2070 patients without asthma (mean age, 61 years; 65.7% women). The prevalence of SA was estimated to be 0.18% to 0.51% of the French adult population. Comorbidities were more frequent in patients with SA (73.9% suffered from cardiovascular disease vs 54.3% in controls; $P < .001$). A total of 58.7% of patients with SA used oral corticosteroids (OCS) in 2012 with a mean intake of 3.3 boxes/year/patient and 9% received ≥ 6 dispensings of OCS. A total of 6.7% were treated by omalizumab. Patients with SA were more frequently hospitalized (33.2% vs 19.7%; $P < .001$), more frequently consulted a general practitioner (97.8% vs 83.9%; $P < .001$) (9.8 ± 6.8 vs 6.2 ± 5.3 consultations/year; $P < .001$), and 31% have consulted a private respiratory physician. Compared with controls, 3-year cumulative mortality was higher in SA (7.1% vs 4.5%; $P = .007$). Direct medical cost was \$9227 versus \$3950 ($P < .001$) mostly driven by medication costs. **CONCLUSIONS:** The prevalence of SA in the French adult population is at least 18 of 10,000. Burden of disease is high with respect to comorbidities, mortality, and asthma-related health care resource use. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1477-87)

Key words: Severe asthma; France; Prevalence; Treatment; Comorbidities; Costs; Mortality

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This research was supported by AstraZeneca, Courbevoie, France.

Conflict of interest: A. Bourdin received fees or funding from AstraZeneca, GSK, Chiesi Pharmaceuticals, Boehringer Ingelheim, Novartis, Roche, Sanofi/Regeneron, and TEVA for consulting activities, participation in scientific committees, and as investigator of clinical trials. C. Fabry-Vendrand, J. Ostinelli, M. Ait-Yahia, and E. Darnal are employees of AstraZeneca, which supported this study. S. Bouée, C. Laurendeau, and I. Bureau are employees of CEMKA, which received grants from AstraZeneca to conduct this analysis. J. Gourmelen has no relevant conflicts of interest. C. Chouaid received fees for attending scientific meetings, speaking, organizing research, or consulting from AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis, Lilly, Novartis, MSD, BMS, and Amgen.

Received for publication July 12, 2018; revised December 20, 2018; accepted for publication December 21, 2018.

Available online January 25, 2019.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.12.029>

Asthma currently affects an estimated 358 million individuals worldwide, posing a substantial burden on health care systems.¹ It is important to have a reliable estimate of the prevalence of severe asthma and an understanding of the disease burden it carries to optimize care pathways for these patients and to improve decision-making and reimbursement policies from the payer perspective. A

Abbreviations used

ALD- Affection de longue durée
 CMUc- Universal Health Coverage
 COPD- Chronic obstructive pulmonary disease
 EGB- Echantillon Généraliste des Bénéficiaires
 GINA- Global Initiative for asthma
 GP- General practitioner
 ICD-10- International Classification of Diseases
 ICS- Inhaled corticosteroids
 LABA- Long-acting β -agonists
 OCS- Oral corticosteroid

better understanding of the landscape of severe asthma in France also has the potential for ensuring effective and equal access to care for all. Over the past few decades, the prevalence of severe asthma has been estimated to be around 5% to 10% of the total asthma population.²⁻⁴ However, the exact prevalence is not known because of the lack of an accurate and consistent definition of severe asthma. In recent population-based studies using administrative and reimbursement databases, patients with severe uncontrolled asthma comprised 2.3% to 3.6% of patients with persistent asthma.^{5,6} Nonetheless, severe asthma accounts for a disproportionate share of asthma-related health care resource use and costs.^{7,8} Such data become of critical importance in the era of biological treatments, as strategies based on these treatments will be expected to reduce the overall burden of severe asthma, and, in particular, obviate the need for oral corticosteroid (OCS) treatment in most patients.^{9,10}

Current definitions of severe asthma are based on a stepwise approach according to medication requirement.¹¹ The Innovative Medicines Initiative international consensus, Global Initiative for Asthma (GINA), and more recently the European Respiratory Society/American Thoracic Society guideline include in the definition of severe asthma not only the requirement for continuous high-dose inhaled corticosteroids (ICS) and long-acting β -agonists (LABA) but also a requirement for OCS for half of the year or more.¹¹⁻¹³ These criteria make it possible to identify individuals with severe asthma in medical databases through their medication prescription.

Administrative and electronic databases afford the opportunity to study large numbers of patients. In France, it has recently become possible to access data from the nationwide claims and hospitalization databases, which enables collection of more representative data than patient registries.^{14,15} Because the information is accurate and exhaustive and can be linked between the claims and the hospitalizations, the Echantillon Généraliste des Bénéficiaires (EGB) database, a 1/97th sample of the whole French population database can be considered as one of the most reliable databases in France for epidemiological studies.

The objective of the present study was to provide accurate information on patients suffering from severe asthma, focusing on disease burden in terms of comorbidities, mortality, health care resource consumption, and associated costs.

METHODS

General design

In this study, we used the permanent beneficiaries sample database (EGB)^{14,16,17} to identify a cohort of patients with severe asthma. The

EGB database is a 1/97th random sample of the French hospital and insurance claims database that, at the time of the study, comprised around 600,000 salaried workers and their relatives (87% of French population) and was fully representative of the French population in terms of gender, age, and mean health care expenditures reimbursed to individual patients.¹⁴ The EGB database contains individual, anonymized information on (1) gender, age, area of residence, and date of death (but not the cause of the death); (2) full health care coverage for chronic illness (affection de longue durée [ALD]; chronic disease, and result in full insurance coverage for all related medical, pharmaceutical, and transport expenses); (3) health care dispensed and refunded in private and public medical institutes, with dispensing dates for drugs and devices, biological and radiological tests, and consultations; and (4) hospital discharge summaries for all stays in public and private medical institutes, corresponding to the 10th version of the International Classification of Diseases (ICD-10) diagnosis and diagnosis-related group.¹⁴ Numerous previous publications^{14,16-18} have illustrated how the EGB database provides an accurate description of the health status of the national population.

This observational study analyzed 2 cohorts, the first of patients with severe asthma and a second cohort of patients without asthma matched for age, gender, and eligibility for Universal Health Coverage (CMUc; a social protection for subjects with a low income and not already covered by a Social Security scheme). These cohorts were identified in the EGB database in 2012 (January 1 to December 31) and followed up until December 31, 2015. Information in the database relating to the preindex period (2006-2011) has also been considered to identify patients with severe asthma and comorbidities.

Subjects

Severe asthma cohort. Identification of patients with severe asthma used an algorithm based on the GINA recommendations.¹¹ Patients were required to have received at least 1 dispensing for omalizumab in 2012 and/or at least 10 dispensings of an association of a medium- or high-dose ICS and a LABA in 2012. The choice of 10 rather than 12 dispensings was based on the hypothesis that certain patients could have been dispensed a prescription in December 2011 that covered the month of January and that others may sometimes have a dispensing for 2 months at the same time (eg, during the holiday period).

Because ICS and LABA can be used for many other conditions than asthma, patients treated with these drugs were classified according to the presence of asthma, chronic obstructive pulmonary disease (COPD), or other respiratory disease identified as a diagnosis related to eligibility for ALD or to a hospital stay. This algorithm defined 3 populations (Figure 1), namely (1) patients with certain severe asthma, (2) patients with COPD or another respiratory disease, but not asthma, and (3) patients affected by potentially severe asthma but more likely responding to the definition of "difficult to treat asthma" or by another respiratory disease. The current analysis focused only on the group with certain severe asthma.

No asthma cohort. The no asthma control cohort consisted of patients aged 18 and over who were matched by age, gender, and advantage of the CMUc to patients in the severe asthma cohort. We excluded from the control cohort any patient with a diagnosis of asthma reported in the database for access to ALD status (full reimbursement coverage), a diagnosis of asthma related to a hospitalization or dispensing of a drug indicated in asthma (Anatomical Therapeutic

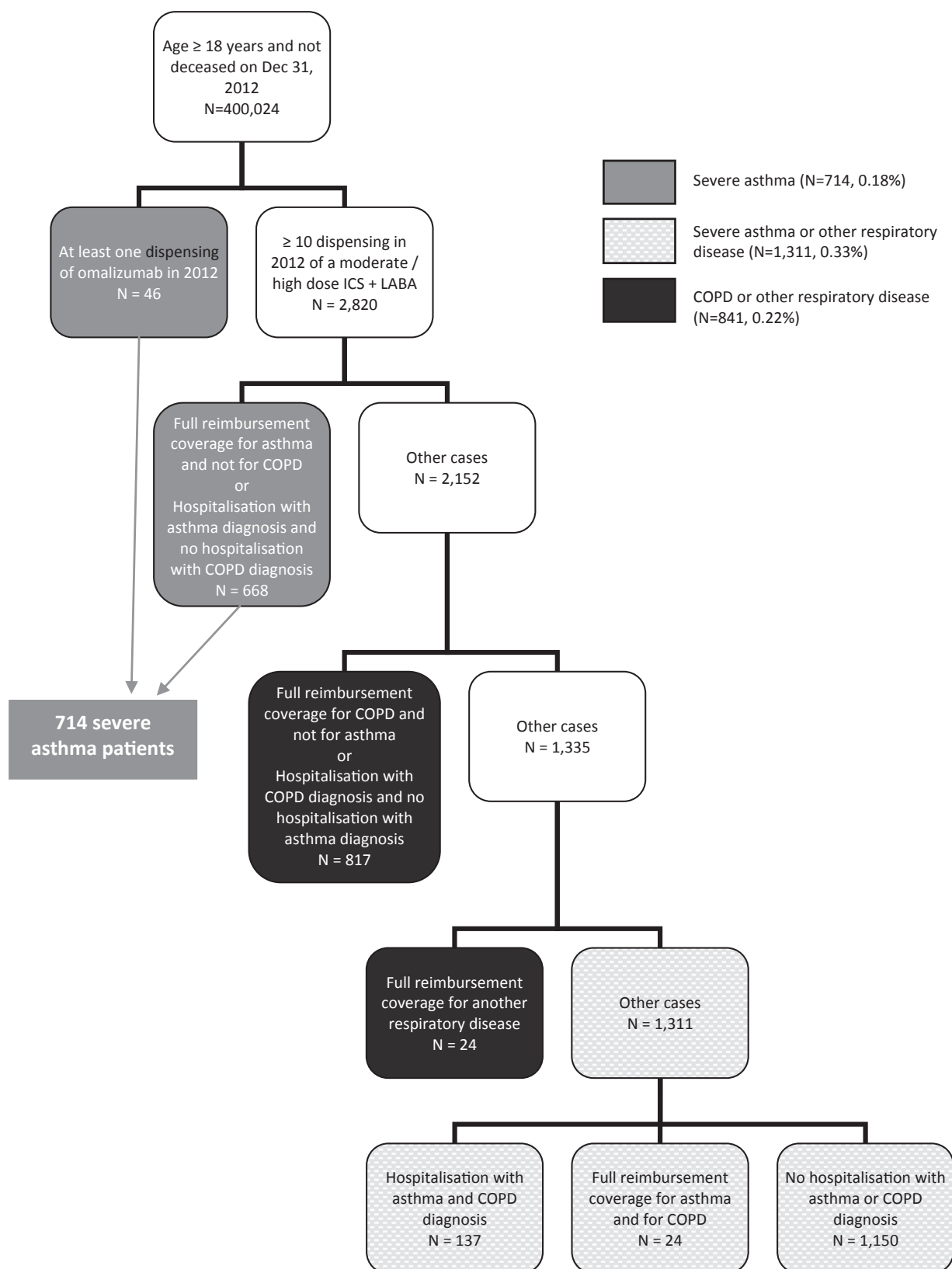


FIGURE 1. Selection algorithm of the severe asthma population. *COPD*, Chronic obstructive pulmonary disease; *ICS*, inhaled corticosteroids; *LABA*, long-acting β -agonists.

TABLE I. Comorbidities

Comorbidity	Patients with severe asthma	Patients without asthma	P*
	N = 690	N = 2070	
Hypertension ^{†‡}	252 (36.5%)	356 (17.2%)	<.001
Dyslipidemia [§]	230 (33.3%)	599 (28.9%)	.03
Diabetes ^{†§}	111 (16.1%)	235 (11.4%)	.001
Obesity [†]	100 (14.5%)	83 (4.0%)	<.001
Cardiovascular disease ^{††§}	510 (73.9%)	1125 (54.3%)	<.001
Cardiac failure ^{††}	28 (4.1%)	47 (2.3%)	.01
Chronic ischemic heart disease ^{††}	47 (6.8%)	93 (4.5%)	.02
Peripheral artery disease ^{††}	18 (2.6%)	38 (1.8%)	.2
Stroke or transient ischemic attack ^{††}	18 (2.6%)	48 (2.3%)	.6
Pulmonary embolism, phlebitis, or thrombophlebitis [†]	11 (1.6%)	16 (0.8%)	.058
Hypertensive cardiopathy [†]	18 (2.6%)	13 (0.6%)	<.001
Osteoporosis ^{†§}	257 (37.2%)	517 (25.0%)	<.001
Glaucoma ^{†§}	61 (8.8%)	141 (6.8%)	.076
Cataract [†]	106 (15.4%)	147 (7.1%)	<.001
Depression ^{††§}	213 (30.9%)	384 (18.6%)	<.001
Gastro-duodenal ulcers, gastritis, or GERD ^{†§}	454 (65.8%)	832 (40.2%)	<.001
Iron deficiency anemia [§]	83 (12.0%)	145 (7.0%)	<.001
Sleep disorders (dispensings of hypnotic and sedative drugs) [§]	161 (23.3%)	296 (14.3%)	<.001
Sleep disorders [†]	52 (7.5%)	35 (1.7%)	<.001

ALD, Affection de longue durée; GERD, gastroesophageal reflux disorder; ICD, International Classification of Diseases.

* χ^2 test.

[†]Comorbidity identified through the relevant ICD-10 disease code associated with a hospitalization.

[‡]Comorbidity identified through the relevant ICD-10 disease code associated with eligibility for ALD status.

[§]Comorbidity identified through the presence of serial reimbursements for dispensings of relevant specific medications.

Chemical classification class R03) in the database between 2006 and 2012.

Data collection

For each eligible patient, information was extracted from the database on demographics (gender and age at the time of index date), reimbursed medication, comorbidities, events, and death. Reimbursed medications of interest were limited to OCS and antibiotics with a specific attention on the seasonality of dispensings of these drugs. The proportion of patients receiving OCS for at least 6 months was determined.

Comorbidities and risk factors of interest included cardiovascular diseases, cardiovascular risk factors (except smoking), osteoporosis, glaucoma, cataract, gastroduodenal ulcers, sleep disorders, and depression. These were identified from 3 sources, namely (1) diagnoses identified with hospitalizations through the relevant ICD-10 disease code, (2) eligibility for ALD status, again through the relevant ICD-10 disease code, and (3) serial reimbursements for prescription of relevant disease-specific medications.

With respect to health care resource consumption, the proportion of patients hospitalized was determined. Among the patients who were hospitalized, the number of hospitalizations, the number of stays in an intensive unit care, the use of mechanical ventilation, and the number of emergency department consultations were analyzed. The proportions of patients with financial aid for a disability leading to a work impairment and of patients with sick leave (and the number of days of leave) were also documented.

Costs (for the year 2012 in \$) were determined from a societal perspective. All expenses related to hospital stays were extracted directly from the database. Nonhospital expenditures were grouped into the following categories: consultations, drugs, laboratory tests,

nursing and other paramedical activities, medical transport, and other expenses. The exchange rate between euros (€) and dollars (\$) was 1.3194 in December 31, 2012 (<https://tauxdechange-euro.fr/archive-devises/2012-12-31/>).

Statistical analysis

All statistical analyses were performed using SAS software version 9.4 (Cary, NC).

The analysis has been performed for the year 2012.

Each patient with severe asthma was matched with 3 control subjects. Data presentation is principally descriptive. Continuous data are presented as mean values $\pm$ standard deviation, and categorical data as frequency counts and percentages. A bilateral probability threshold of 0.05 was used to determine statistical significance. Costs were compared using the Wilcoxon nonparametric test.

For the analysis of deaths, time to events of interest was evaluated using the Kaplan Meier method. Mortality was also assessed after an adjustment on comorbidities that were significantly different in proportions, between the severe asthma population and the control group, by using a propensity score.

Based on a preliminary analysis, it was expected that approximately 800 subjects would be available in the database to perform the analysis with sufficient precision. This number was expected to provide sufficiently accurate estimates of the prevalence of comorbidities and of mortality rates. The database was thus considered to be large enough to achieve the objectives of these analyses.

Ethical considerations

Because this was a study of an anonymized database and had no influence on patient care, ethics committee approval was not required.

TABLE II. Treatments in 2012 (oral corticosteroids and antibiotics)

	Patients with severe asthma	Patients without asthma	P
	N = 690	N = 2070	
At least 1 dispensing of oral corticosteroids	405 (58.7%)	378 (18.3%)	<.001*
If yes, number of dispensings (mean ± SD)	3.3 ± 3.1	1.8 ± 1.8	<.001†
At least 1 dispensing of antibiotics	526 (76.2%)	834 (40.3%)	<.001*
If yes, number of dispensings (mean ± SD)	3.3 ± 2.8	2.0 ± 1.7	<.001†

SD, Standard deviation.

*Wilcoxon test.

† χ^2 test.

RESULTS

Study population

Of the 400,024 adult subjects included in the EGB database, 714 (0.18%) were identified with severe asthma. Of these, 690 patients could be matched to 2070 patients without asthma. These constitute the study populations for this analysis.

Prevalence of severe asthma

In this national database analysis, we observed that 0.18% of adults in the EGB database fulfilled the criteria for severe asthma. Extrapolated to the total French adult population (49,430,000 individuals in 2012), this would suggest that there are at least 88,000 patients with severe asthma in France.

Sociodemographic data and comorbidities

Around two-thirds of patients with severe asthma were women (65.7%) and the mean age was 61 years. Compared with patients without asthma, patients with severe asthma more frequently presented cardiovascular risk factors, namely hypertension (36.5% vs 17.2%; $P < .001$), dyslipidemia (33.3% vs 28.9%; $P = .03$), diabetes (16.1% vs 11.4%; $P = .001$), and obesity (14.5% vs 4.0%; $P < .001$) (Table I).

All studied cardiovascular conditions observed were more frequently documented in patients with severe asthma than in subjects without asthma. The differences were statistically significant for cardiac failure (4.1% vs 2.3%; $P = .01$), chronic ischaemic heart disease (6.8% vs 4.5%; $P = .02$), hypertension (36.5% vs 17.2%; $P < .001$), and hypertensive cardiomyopathy (2.6% vs 0.6%; $P < .001$). The proportion of patients with severe asthma having any cardiovascular disease was higher (73.9%) than that of patients without asthma (54.3%) ($P < .001$).

Other noncardiovascular comorbidities were also significantly more frequent in severe asthma than in patients without asthma, notably osteoporosis (37.2% vs 25.0%; $P < .001$), cataract (15.4% vs 7.1%; $P < .001$), depression (30.9% vs 18.6%; $P < .001$), gastroduodenal ulcers and oesophageal reflux (65.8% vs 40.2%; $P < .001$), iron deficiency anemia (12.0% vs 7.0%; $P < .001$), and sleep disorders (7.5% vs 1.7%; $P < .001$). In addition, patients with severe asthma were more frequently treated with hypnotic or sedative drugs between 2006 and 2011 (23.3% vs 14.3%; $P < .001$).

Treatments

Overall, 58.7% of patients with severe asthma and 18.3% of patients without asthma had been treated with OCS ($P < .001$) (Table II). Patients with severe asthma treated with OCS were dispensed these drugs on average 3.3 times in 2012, compared with 1.8 times for patients without asthma ($P < .001$). The pattern of OCS use is presented in Figure 2. If we assume that 1

dispensing corresponds to a month of treatment, then at least 9% of the patients with severe asthma were treated with OCS for 6 months or more in 2012. A total of 6.7% of patients were treated by omalizumab.

The proportion of patients treated with antibiotics in 2012 was also higher for patients with severe asthma (76.2%) compared with patients without asthma (40.3%) ($P < .001$). Patients with severe asthma also had a higher number of dispensings of antibiotics than patients without asthma (3.3 vs 2.0; $P < .001$).

The analysis of the proportion of patients with severe asthma treated with OCS and antibiotics, according to the quarter of each year from 2012 to 2015, showed a clear seasonal pattern (Figure 3) peaking in winter.

Health consumptions

More patients with severe asthma attended a general practitioner's (GP) outpatient clinic than patients without asthma (97.8% vs 83.9%; $P < .001$) (Figure 4), and they consulted GPs more frequently (9.8 ± 6.8 vs 6.2 ± 5.3 ; $P < .001$). The proportions of patients who consulted a lung specialist in a private setting or a specialist in a public hospital were also significantly higher for the severe asthma cohort compared with patients without asthma, respectively, 31.0% vs 1.7% ($P < .001$) and 28.3% vs 16.3% ($P < .001$), as well as the number of patients who consulted a nurse (55.7% vs 35.2%; $P < .001$) or a physiotherapist (30.6% vs 19.1%; $P < .001$).

The proportion of patients with severe asthma who were hospitalized was significantly higher than in patients without asthma (33.2% vs 19.7%; $P < .001$) (Figure 4). They also tended to be more frequently admitted to the emergency department (10.4% vs 4.8%; $P = .052$). The mean number of hospitalizations in 2012 was similar in both groups (2.0 ± 2.8 vs 2.7 ± 8.4 ; $P = .8$) as well as the proportion of hospitalizations that included intensive unit care stays (2.3% vs 1.5%; $P = .8$).

The overall annual cost from a societal perspective for patients with severe asthma was $\$9227 \pm \$9969$ versus $\$3950 \pm \$7858$ for patients without asthma ($P < .001$), corresponding to an excess cost of $\$5276$ (Figure 5). The difference was mainly driven by outpatient costs ($\$7230$ and $\$2664$; $P < .001$), but a significant difference was also observed for private ($\$454$ and $\$377$; $P = .02$) and public hospitalization costs ($\$1542$ and $\$910$; $P < .001$).

The difference in outpatient expenditures between patients with severe asthma and patients without asthma was observed for nearly all categories of health consumptions (except dentist consultations) (Figure 5). The most important difference was related to pharmacy expenditure ($\$4146 \pm \$5651$ for patients with severe

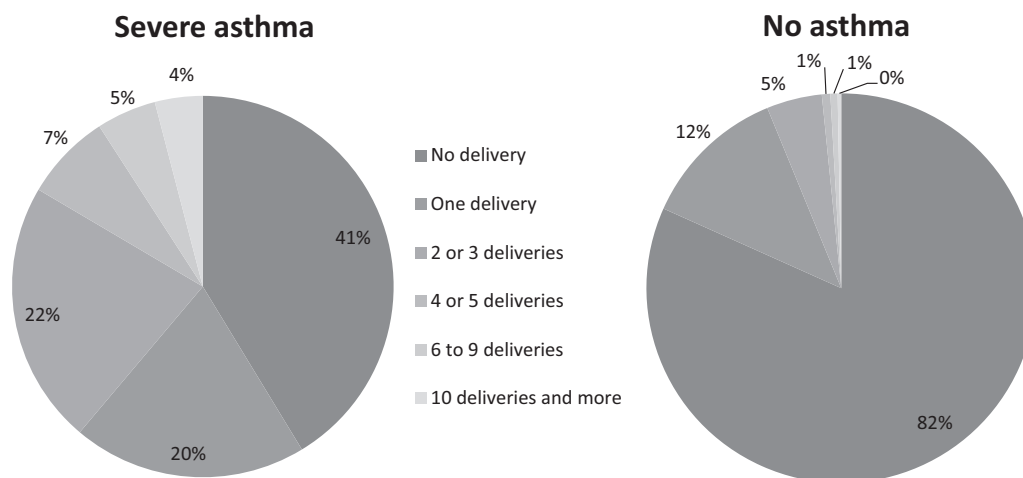


FIGURE 2. Number of dispensings of oral corticosteroids in 2012.

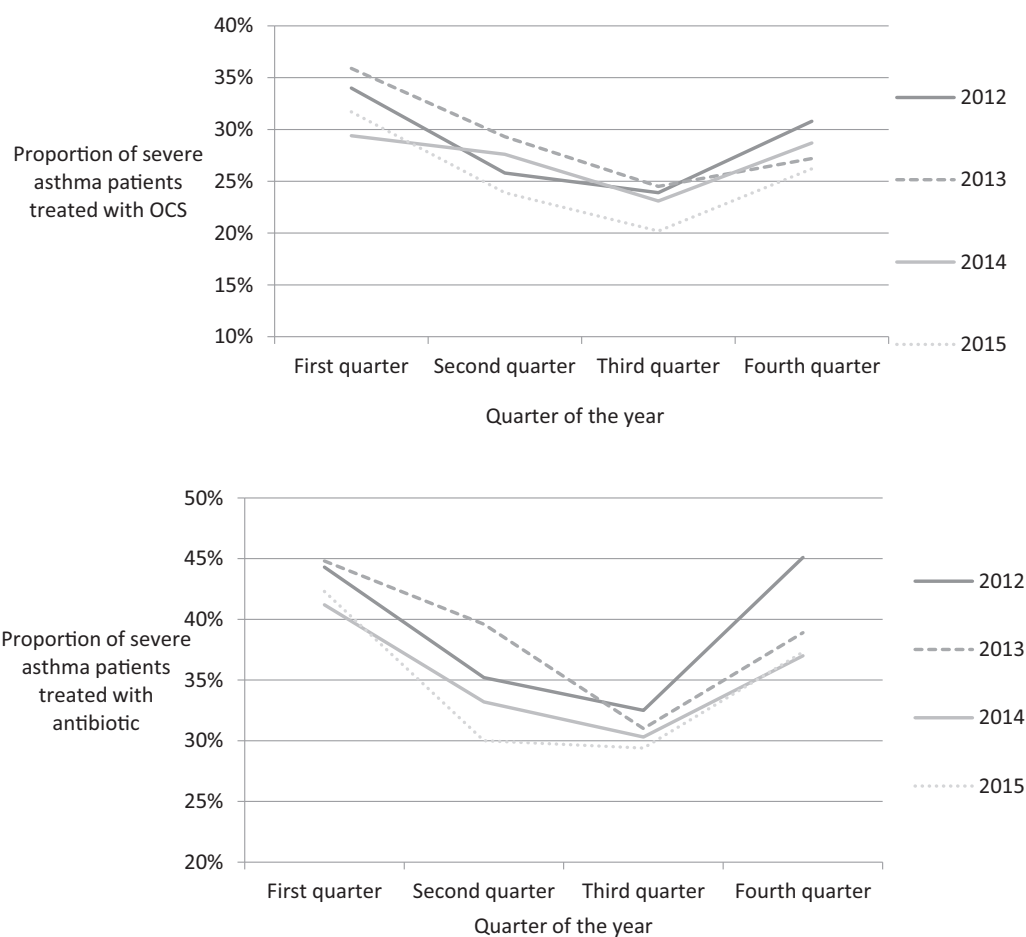


FIGURE 3. Proportion of patients with severe asthma treated with OCS and antibiotics according to the quarter and the year. OCS, Oral corticosteroid.

asthma and $\$847 \pm \$2132$ for patients without asthma; $P < .001$). The proportion of patients with sick leaves was higher in the severe asthma cohort than in the no asthma controls (12.6% vs 8.1%; $P = .0004$), as was the proportion of patients receiving financial aid for a disability (5.1% vs 1.4%; $P < .001$).

Mortality

The cumulative mortality rate over the 3 years of follow-up was higher in patients with severe asthma (7.1% vs 4.5%; $P = .007$) (Figure 6), even though the 2 cohorts were matched for age, gender, and a proxy for precarity: the CMUc.

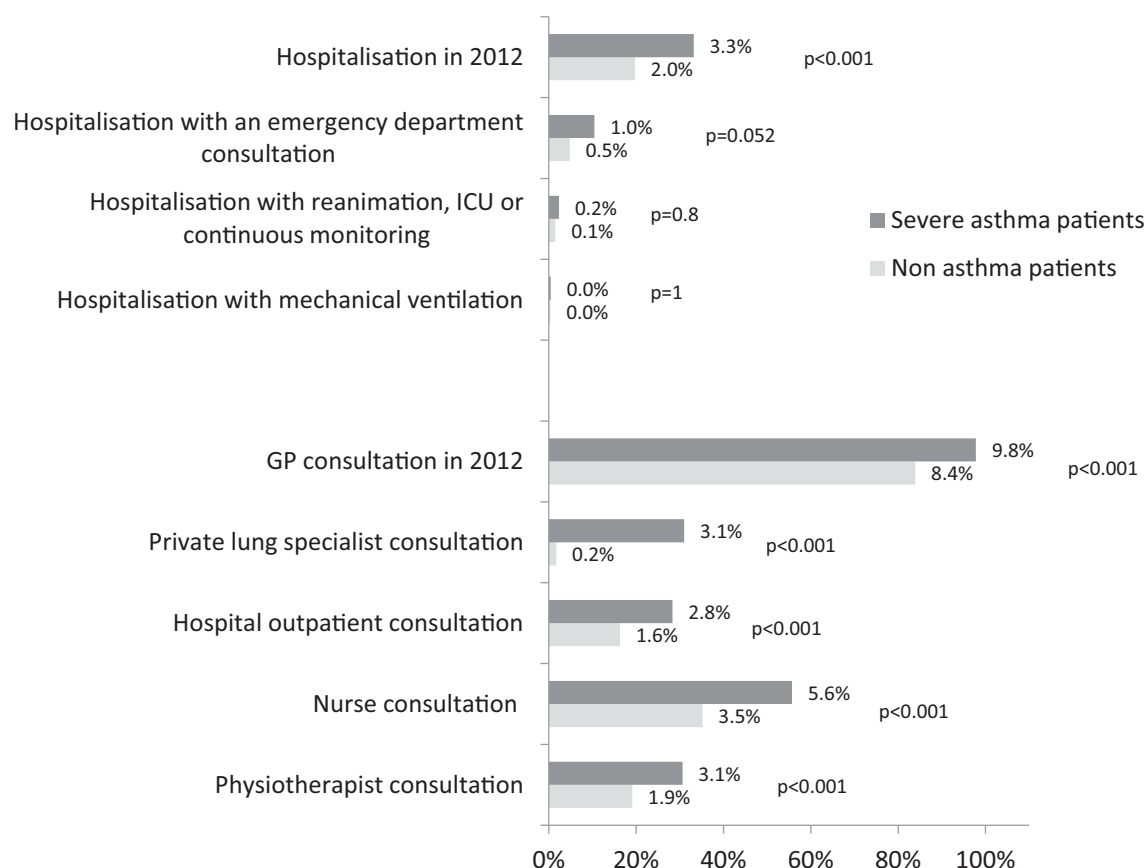


FIGURE 4. Hospitalizations and consultations in 2012. *GP*, General practitioner; *ICU*, intensive unit care.

A propensity score of belonging to the severe asthma population or to the control was calculated with a logistic regression on the following characteristics: heart failure, chronic ischemic heart disease, peripheral artery disease, stroke or transient ischemic attack, pulmonary embolism/phlebitis/thrombophlebitis, hypertension, osteoporosis, glaucoma, cataract, depression, gastro-duodenal ulcers/gastritis, iron deficiency anemia, sleep disorders, and dispensings of hypnotic and sedative drugs. After adjustment on this propensity score, the relation between severe asthma and death was not statistically significant ($P = 0.36$).

DISCUSSION

Prevalence

In this national database analysis, we observed that 0.18% of adults in the EGB database fulfilled the criteria for severe asthma, that is, 88,000 patients in France.

However, the algorithm used is likely to have missed certain patients with severe asthma. For some individuals in the database, it was not clear from the available information whether these subjects actually had asthma and not another respiratory disease, such as COPD or had multiple respiratory diseases. These 1311 patients were classified as “severe asthma or other respiratory disease” (Figure 1). If these patients all had severe asthma, the prevalence would rise from 0.18% to 0.51%. Extrapolated to the total French adult population, the estimated total number of people with severe asthma would in this case be

around 250,000 individuals. An intermediate estimate could be 0.33%, that is, 163,000 adult patients in France. This estimate takes into account a 46% proportion of patients with severe asthma among those identified as “severe asthma or other respiratory disease” (46% is the percentage of patients with asthma among patients with a respiratory disease and was obtained by dividing the number of certain patients with severe asthma [714] by the total of certain respiratory diseases identified [714 + 841 COPD or another respiratory disease]).

Previous epidemiological studies in Europe and elsewhere^{5,19-24} have estimated the prevalence of severe asthma to be between 0.1% and 0.6% of the adult population. Our range of 0.18% to 0.51% is consistent with these previous findings. A limited number of previous studies have assessed the prevalence of severe asthma in France. A study performed in 2006, based on a random sample of 21,000 individuals^{25,26} who completed and returned a paper questionnaire, estimated the prevalence of all asthma to be 6.7% of the French adult population and that of severe asthma to be 0.6%. This estimation was slightly higher than the present one. However, the methodology used was different and the biases associated with epidemiological data collected from self-report in terms of participation bias and recall bias are well known. Our definition was more reliable because it is based on the objective criterion of dispensing of at least 10 prescriptions of medium- or high-dose ICS and LABA, which is a specificity of severe asthma according to the GINA guidelines definition.¹¹ Because of the exclusion from the prevalence estimate of patients with potentially comorbid

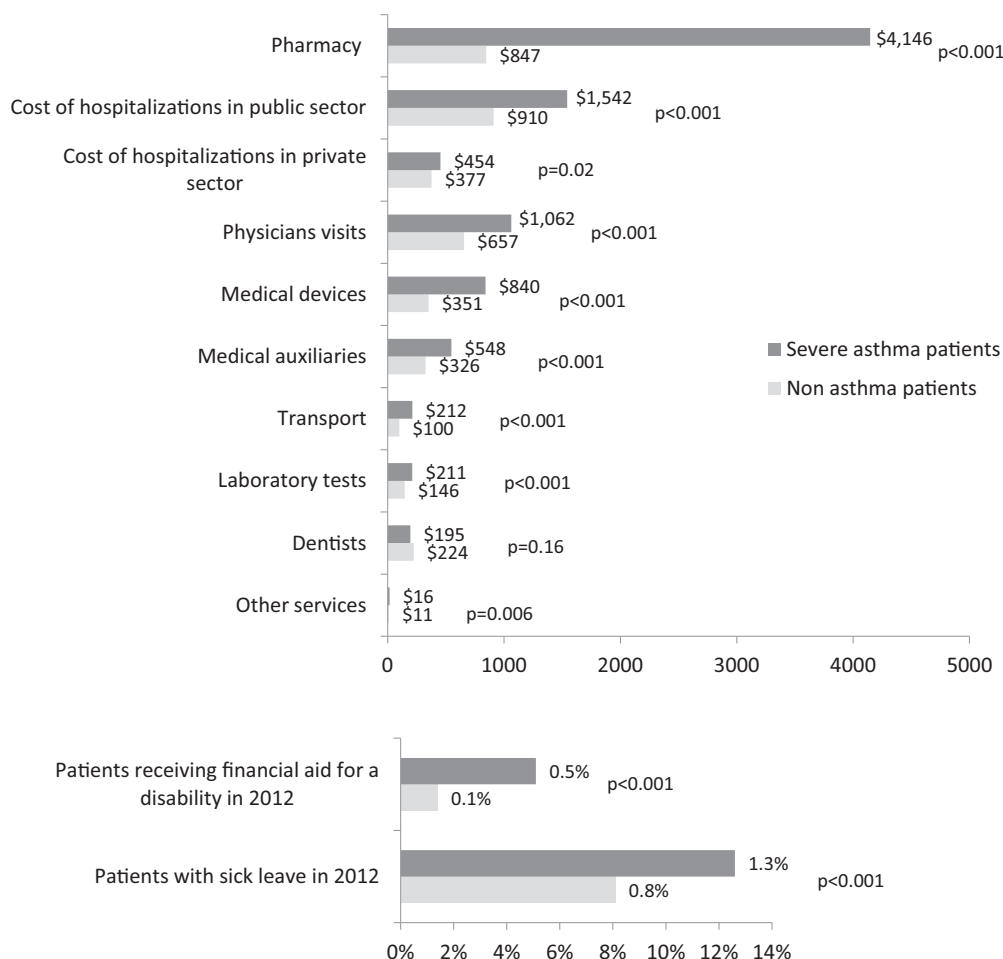


FIGURE 5. Costs from a societal perspective, sick leaves, and aid for disability.

conditions for which ICS/LABA are also prescribed, this was a conservative estimate. This choice, which optimizes the specificity of the measure at the expense of sensitivity, was made to obtain more credible data. In the era of biological treatments, the lower limit of the range is more meaningful for the payer as it will be more helpful to assess the gap between treated and eligible but untreated patients.

Comparator group

We have compared the severe asthma patients group to a population of subjects not affected by asthma. The differences between both populations could therefore be attributed to the disease itself (asthma) or to the severity of the disease or both. To explore this point we could have also compared the population of patients with severe asthma with a population of patients with asthma who would not have the criteria for a severe disease. However, such a control group is biased for the following reasons. The EGB database does not record all diseases of subjects, but only long-term severe diseases that lead to a 100% reimbursement for health consumptions. Beyond this, we cannot identify asthma with the drug treatments, because most of these drugs are also used in COPD. Therefore, the EGB cannot

identify a representative population of patients suffering from nonsevere asthma.

Treatment patterns

We found that at least 9% of patients with severe asthma were treated with OCS for more than half of the year in 2012. In addition, 6.7% of the patients were treated by omalizumab, which was the only biological drug available in France at that time. This implies that many patients who could potentially have benefited from this treatment were not prescribed it, although it is possible that the percentage of patients with severe asthma treated by this drug has increased since 2012. Of note, omalizumab is subject to restrictions of prescription: only by respiratory physicians. In parallel to our observation that approximately 31% of patients with severe asthma consulted a respiratory physician (in a private setting in the year), this may indicate the room for improvement for accessing these drugs qualified for “exceptional drugs” in France. This may have direct consequences in the care pathway for patients with severe asthma. Initiatives headed by academic and nonacademic stakeholders are currently developed materialized by the release of national and European registries.

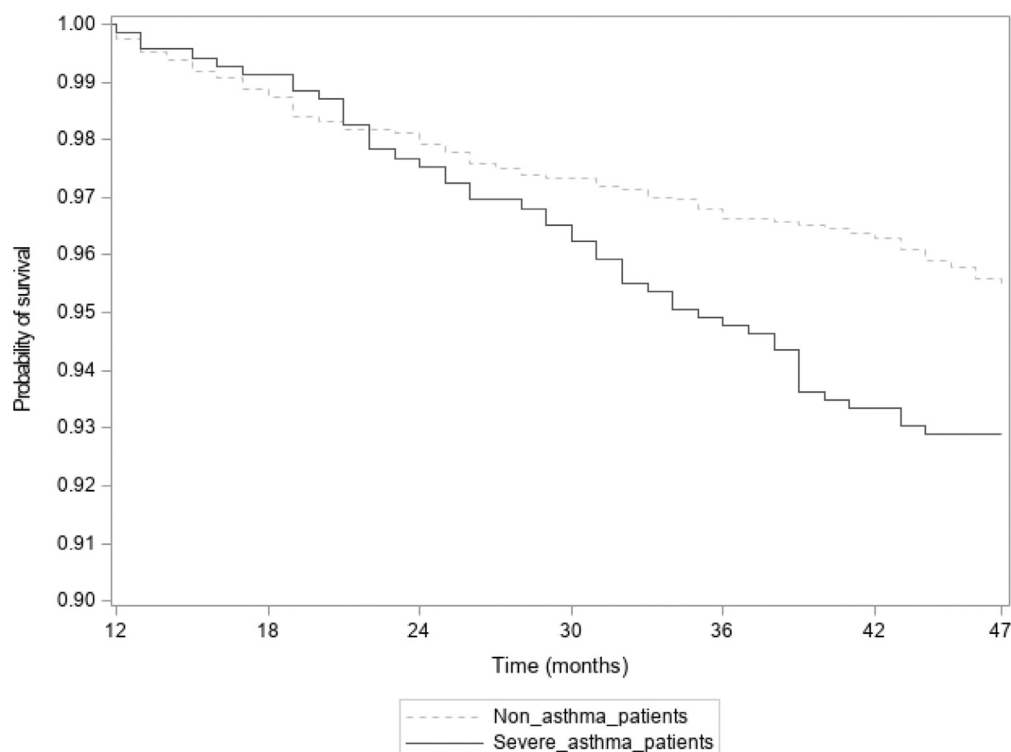


FIGURE 6. Survival curve for death in subjects with severe asthma and those without asthma.

There was a clear seasonal pattern in use of OCS and antibiotics, with a peak in winter. Other studies have found that respiratory virus infections increase in winter.^{27,28} The role of such infections in asthma exacerbations has been emphasized in previous studies, and the management of these exacerbations may explain the higher use of OCS in winter.^{29,30}

A very high proportion of patients were treated with antibiotics (76.2% with at least 1 prescription dispensing in 2012). However, bacterial infections have been shown to be no more common in severe asthma than in the general population.³¹ This high rate of antibiotic use could be deleterious,³² for example, interfering with the availability of asthma medication through the effects of certain antibiotics on cytochrome P450 drug-metabolizing enzymes.³³ It should be acknowledged that in this survey, it is impossible to know if these dispensed drugs were really taken or if they were prescribed as rescue medications as part of a written and shared management plan. Whether OCS should be part of such a plan or not is still debated.¹¹ Multifactorial heterogeneities in the management of severe asthma are expected and may rely at least in part on physician beliefs, the patient's preferences but also accessibility to health care resources.

Mortality

Asthma mortality has decreased during the last 20 years, probably owing to improved management and treatment, particularly due to the beneficial effects of ICS.³⁴ A recent Swedish study has concluded that mortality in individuals with asthma had now fallen to that of the Swedish general population.³⁵ In contrast, a Canadian study has reported an all-cause mortality rate ratio of 1.3 for individuals with asthma

compared with the general population.³⁶ Similarly, another study conducted in Finland reported a significantly increased mortality rate ratio of 1.25.³⁷ In our study, when compared with patients without asthma, the 3-year overall mortality rate was significantly higher in patients with severe asthma compared with patients without asthma. Other surveys have reported an increased risk of death in patients with severe asthma, and a few deaths have been documented in nearly all large clinical trials with biological therapies conducted in this population whereas they rarely overtook 52 weeks.^{9,10,38} A recent prospective follow-up study of patients with OCS-dependent asthma in France has provided similar information.³⁹ Interestingly, it seems that people with asthma are now dying less from asthma attacks and more from associated comorbidities, among which cardiovascular diseases seem predominant.^{40,41} This last result is in line with our finding that after adjusting on several comorbidities and risk factors with a propensity score, it appears that the increased mortality of patients with severe asthma is no longer statistically significant. This result suggests that the higher mortality of patients with asthma is rather linked to the comorbidities than to asthma itself.

Comorbidities

Several studies have investigated comorbidities in patients with asthma compared with subjects without asthma.

Several studies have highlighted the increased frequencies of some comorbidities that systemic corticosteroids are a common cause of adverse events in patients exposed to regular doses of OCS.^{11,40,42-45} Among the most frequently reported comorbidities were cardiovascular diseases, osteoporosis, gastrointestinal disorders, sleep disturbance, hypertension, diabetes, fractures, and cataracts. Some of these may contribute to poor asthma

control,^{11,46} including obesity, gastroesophageal reflux disease, and psychiatric disorders. GINA guidelines recommend investigating systematically (even in the absence of any evocative symptom or other risk factor) the possibility of chronic sinusitis, obesity, gastrointestinal disorders, obstructive sleep apnoea, and psychological or psychiatric disorders, which may compromise asthma control or contribute to symptoms. Active management of any identified comorbidities is recommended with the goals of reducing symptom burden, improving quality of life, and limiting the risk of medication interactions.¹¹

Costs

Disease-related cost is usually classified into direct, indirect, and intangible costs. Direct costs include disease management (consultations, hospital admissions, medications, etc.). Indirect costs include work-related losses (sick leaves, early or permanent disability, absenteeism, etc.) and early mortality. Intangible costs are those related to unquantifiable losses, such as the decrease in quality of life. Our study focused on direct and indirect costs only, but we did not attempt to quantify indirect costs because it is not recommended by the French Health Technology Assessment.⁴⁷

In their recent (2017) review on the costs and social impact of asthma, Nunes et al⁴⁸ documented the costs of asthma in several European countries. The authors estimated that the annual direct and indirect *per capita* costs related to asthma were over \$US 2000 (which is equivalent to \$2496 in 2012) in England and Germany; between \$US 1500 (\$1872 in 2012) and \$US 2000 (\$2496 in 2012) in France, Italy, and Norway; and below \$US 1500 (\$1872 in 2012) in other European countries. In our study, the direct cost of patients with severe asthma in 2012 was \$9312. As the cost was \$3945 in the control group, the excess cost of asthma can be estimated at \$5268, which is much higher than the cost reported by Nunes et al.⁴⁸ However, our study only focused on severe asthma (and a treatment by omalizumab was one of the definition criteria), which may explain the higher cost. A large rise in the cost of asthma with increasing severity of the disease has been reported in previous studies, with a cost difference ranging from 2.4-fold to 5-fold according to the study.^{8,49}

In a study published by Cisternas et al⁵⁰ in the United States, the total annual *per capita* costs of asthma averaged \$4912 (\$6918 in 2012), with direct and indirect costs accounting for \$3180 (\$4479 in 2012) (65%) and \$1732 (\$2440 in 2012) (35%), respectively. The largest components of direct costs were medication (\$1605 [\$2261 in 2012] [50%]), hospital admissions (\$463 [\$652 in 2012] [15%]), and nonemergency department outpatient visits (\$342 [\$482 in 2012] [11%]). These costs are of similar magnitude to the present study, although all grades of asthma severity were included. A retrospective analysis of a national US administrative claims database focused on persistent asthma and severe asthma.⁵¹ Unadjusted mean annual asthma-related costs in severe asthma was \$6496 in 2012, with a medication cost of \$4545, which is slightly higher than our findings. Additional costs due to OCS-induced comorbidities could not be estimated.

The incremental cost of severe asthma that we estimated at \$5268 was largely driven by medication and hospitalizations that contributed respectively to \$3294 and \$707. In an extensive review of 68 studies, Bahadori et al⁸ also found that hospitalization and medications were the most important drivers of direct

costs. Of the pharmaceutical drugs available for asthma treatment, omalizumab is the most expensive and may be a major driver for the increased cost in patients treated with this drug. This situation will certainly be significantly affected by the arrival of other biological therapies for severe asthma (mepolizumab, reslizumab, dupilumab, benralizumab), as well as of bronchial thermoplasty. In this context, a recent National Institute for Health and Care Excellence (NICE) appraisal proposed stopping rules for mepolizumab based on the efficacy of this drug, its price, and its cost effectiveness.⁵²

Bias

This study performed with a French claim database representative of the French population¹⁴ avoids the biases of observational studies such as selection bias and information bias. Moreover, the risk of attrition can be considered as insignificant because there are very few reasons for a subject to leave one of the 3 main public health care insurance schemes.

Nonetheless, there are some limitations to the use of this claims database.

The major limitation of our study is that, unless a patient is eligible for ALD or has been hospitalized, there is no explicit information on diagnosis. All the patients identified here are identified through the treatment criterion (ICS/LABA in 99% of cases) and there is no information on EGB on why they were prescribed.

Another limitation is the lack of precise clinical information, especially clinical and biological details, as well as a lack of information on major cardiovascular risk factors such as smoking status, body mass index, blood pressure, and cholesterol values that could affect patient prognosis. The risk of miscoding cannot be excluded, but it is considered as infrequent and without systematic errors.

Conclusions

The prevalence of severe asthma in the French adult population is at least 18 of 10,000. The findings of this study emphasize the burden of severe asthma, in terms of elevated comorbidity rates, cost, and mortality. This highlights the needs for new efficacious treatments and more elaborated and identified care pathways that could lead to improved symptom control and reduce the need for OCS.

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