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Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: the RESONANCE study

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ABSTRACT

Word Count: 300

Objective: To characterize uncontrolled severe asthma and compare the disease burden with the general and asthmatic populations.

Design: Retrospective observational study using a national sample of a French healthcare database (*Echantillon Généraliste des Bénéficiaires [EGB])*.

Setting: The EGB, an anonymized permanent sample of health insurance databases, representing 1/97th of the French population.

Participants: Patients (≥12 years) were selected in year 2014 and followed 2 years. A cohort of patients with uncontrolled severe asthma was defined using an algorithm based on peer-reviewed literature and Global Initiative for Asthma recommendations. Index date was the occurrence of the first marker of uncontrolled asthma. This cohort was matched with 2 control cohorts (general population and asthmatic controls) on baseline characteristics-based propensity scores.

Main outcomes measures: Mortality, healthcare use, and associated costs were studied in the 2 years of follow-up.

Results: Among 467,716 individuals in the EGB, 16,588 asthmatics were identified, including 739 (4.5%) with uncontrolled severe disease. The survival probability at 2 years for patients with uncontrolled severe asthma (92.0%) was lower than in the general population cohort (96.6%; relative risk of death: 2.35; 95% confidence interval: 1.70-3.29; *P*<0.0001) and tended to be lower than in the control asthmatic cohort (94.3%; *P*=0.07). Emergency department visits and hospitalizations were higher in patients with uncontrolled severe asthma than in the general population (64.7% vs 34.9%; *P*<0.0001) and asthmatic controls (64.7% vs 55.2%; *P*=0.0002). Other components of healthcare use (medical and paramedical visits, medications) were increased in patients with uncontrolled severe asthma compared with

control populations. These increases translated into higher costs (*P*<0.0001 for both comparisons).

Conclusions: This study demonstrates the huge burden of uncontrolled severe asthma in terms of mortality, morbidity, and healthcare resource consumption compared to other patients with asthma and the general population, and emphasizes the importance of appropriate management in this high-risk population.

Strengths and limitations of this study:

- The study was conducted using a well-recognized and robust populational medical administrative database that confers many advantages, such as the completeness of mortality data and comprehensiveness of healthcare reimbursed for all patients.
- This is the first study to specifically compare uncontrolled severe asthmatic patients with the overall asthmatic population.
- Comparability of studied groups was ensured by careful matching process.
- The lack of clinical data was mitigated by the use of a comprehensive algorithm to identify the uncontrolled severe asthmatic population with great care in the definitions of asthma, severity, and control to ensure the accuracy of the cohorts.
- The criteria requiring continuous insurance coverage may have resulted in a marginally lower number of younger patients being included due to student-specific insurance offered during school years.

INTRODUCTION

Asthma is one of the most common chronic diseases and is a major cause of morbidity. This heterogeneous disease is characterized by its chronic inflammatory nature which can lead to airway remodeling and presents with varied levels of severity and control. While a majority of asthma patients have mild to moderate disease according to Global Initiative for Asthma (GINA) criteria, between 3% and 10% present a severe asthma, which may be life-threatening, particularly due to severe and potentially fatal exacerbations.[1,2] Despite implementation of an optimal management strategy, many patients with severe asthma are not able to achieve disease control, leading to poor quality of life and significant social and health burdens. Asthma therefore represents an important public health issue given its impact on work productivity (ie, absenteeism and presenteeism) and the costs associated with disease management and healthcare resource utilization.[3–7]

In the context of the rapidly evolving landscape of expensive GINA step 5 asthma treatments, it is crucial to generate up-to-date data on the real-life population burden of uncontrolled severe asthma in adolescents and adults and to understand the relative impact of the disease on severe asthma patients compared to the general and to non-severe asthmatic populations. The framework of the French Health Data Hub project provided the opportunity to access the public medico-administrative database to address this specific issue.

The RESONANCE study was undertaken to: (1) characterize uncontrolled severe asthma in patients aged 12 years and older, and (2) compare the disease burden in terms of mortality, healthcare utilization, and associated costs within this population to two series of matched controls from the general population and the asthmatic population (ie total asthmatic population excluding those with uncontrolled severe asthma).

METHODS

Study Design

A retrospective, non-interventional cohort study was carried out using a large populational database from France, the *Echantillon Généraliste des Bénéficiaires* (EGB). All individuals aged 12 years and over in the EGB were included in the source population. A cohort of adolescent and adult patients who had uncontrolled severe asthma during 2014 were identified. Their index date was the date of the first event identifying non-control during 2014. Two control cohorts were defined, one from the general population and another of patients with asthma. For each control selected, the index date assigned was the calendar index date of respective matched patients from the uncontrolled severe asthma cohort.

Historical information on comorbidities, healthcare use, and treatments received were collected in the 5 years preceding the index date to assess baseline characteristics. Cohorts were followed for 2 years after the index date to assess the outcomes of interest (Figure 1).

Data sources

The EGB is an anonymized permanent sample of health insurance databases representing 1/97th of the entire French population.[8,9] Given the universal healthcare system in France, the EGB is a sizeable and representative sample of all subjects covered by various social security schemes and now includes nearly 660,000 beneficiaries.

The EGB contains information on demographics (age, sex, area of residence, etc.); outpatient care reimbursement (including drug dispensing); medical care and reimbursement received in outpatient and hospital settings; specific information on the right to universal supplementary health coverage (CMU-c); whether beneficiaries are affected by a long-term condition (*affection de longue durée*; ALD); and the date of death. The database benefits from the interlinkage of several administrative data sources, thereby allowing an assessment of beneficiaries' healthcare utilization over time.

Subjects

Patients with uncontrolled severe asthma were identified using an algorithm based on events occurring in 2014 (Figure S1, Supplementary File). This algorithm was designed following a literature review,[10–12] and GINA management recommendations,[13] in collaboration with an expert scientific committee composed of 3 respiratory specialists.

Patients with evidence of chronic obstructive pulmonary disease (COPD), identified through International Classification of Diseases, 10th Revision (ICD-10) or ALD codes, were excluded (see Supplementary File).

General population controls were randomly selected among all individuals, besides uncontrolled severe asthmatics, present in the EGB in 2014. Controls were eligible to be matched with patients in the uncontrolled severe asthma cohort if they had the same age, sex, and CMU-c status at index date. Up to 3 controls per case were selected. Matching quality was assessed by comparing standardized differences between both cohorts.

Individuals in this control cohort were randomly selected within the total asthmatic population present in the EGB in 2014, excluding those with uncontrolled severe asthma. Individuals were matched with uncontrolled severe asthmatics on a 1:1 ratio using propensity scores incorporating 45 variables recommended by the expert scientific committee, including sociodemographic characteristics, comorbidities, and healthcare history prior to index date. Standardized differences were used to assess matching quality.

Collected data and outcomes

The following sociodemographic and clinical characteristics were considered:

- In the 5 years prior to index date: comorbidities, treatments received, healthcare utilization (medical visits, emergency department [ED] visits, hospitalizations)
- At index date: age, sex, CMU-c status
- During follow-up:

- Date of death, if applicable
- Drugs of interest: Asthma treatments and other classes of interest (see Supplementary File)
- Healthcare utilization: Medical and paramedical visits (general medicine, respiratory specialists, otolaryngology, nursing support, physiotherapy), ED visits, and hospitalizations (all-cause and asthma-related)
- Direct medical costs associated with medications and healthcare use (outpatient and hospital settings)

The primary objective of this study was to assess the number and proportion of uncontrolled severe asthmatic patients aged 12 and older. Sociodemographic and clinical characteristics were provided for this population.

The secondary objective was to assess mortality and survival probability, healthcare use and associated costs in the 2 years after index date in the uncontrolled severe asthma cohort compared to the two matched control cohorts (general population and asthmatic controls).

Statistical analyses

Continuous variables were described using means, standard deviations, medians, and ranges, whilst categorical variables were described as frequencies and 95% confidence intervals (95% CIs).

Crude cumulative all-cause mortality rates at 2 years were obtained for all cohorts using the Kaplan-Meier methodology, whereby the probability of survival from index date through follow-up was estimated. The comparative analyses of mortality, healthcare utilization, and associated costs between the primary cohort and matched controls were conducted using Student's *t*-tests or Mann-Whitney tests for quantitative variables according to their distribution and chi-square tests for qualitative variables. A post-hoc analysis using a Cox regression model was built to compare mortality between the uncontrolled severe asthmatic cohort and general population. The final model included the following variables: population (uncontrolled

severe asthmatic cohort vs general population), age, history of cardiovascular disease, diabetes, psychiatric disease, and cancer comorbidity per the Charlson comorbidity index score. Interactions between the variable "population" and other covariates included in the model were tested. Costs were adjusted to 2018 Euros (€; date of data access). All analyses were performed using the SAS 9.4 software package (SAS Institute, Cary, NC, USA).

Ethical considerations

The data considered as part of this study were anonymized to ensure confidentiality at the patient level. Data handling, processing, and analysis were carried out in alignment and with authorizations from an independent committee (*CEREES, Comité d'Expertise pour les Recherches, les Études et les Évaluations dans le domaine de la Santé*; favorable opinion on June 14, 2018; TPS 31996) and from the French National Data Protection Agency *(CNIL, Commission Nationale de l'Informatique et des Libertés*; Authorization DR-2018-097).

Patient and Public Involvement Statement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Population selection

Of the 467,716 adolescents and adults present in the EGB, a total of 16,588 asthmatic patients were identified and 5,025 of these exhibited a marker of uncontrolled disease in 2014 (Figure S1). Among these, 739 uncontrolled severe asthmatic patients were identified (57% female; mean age: 62.0 years; 10.0% with CMU-c).

A total of 2,217 matched individuals were selected to build the control cohort from the general population. The control asthmatic population (all asthmatic patients excluding those with uncontrolled severe asthma) included 739 patients matched to uncontrolled severe asthmatic patients using propensity scores (53.0% women; mean age: 63.2 years; 7.7% with CMU-c, data not shown). The majority of the 45 variables defined for matching were successfully balanced (see Supplementary File).

Mortality

In total, 59 uncontrolled severe asthmatic patients died in the 2-year follow-up period. The probability of survival at 2 years in this cohort was 92.0%, which is statistically significantly lower than that observed in the matched control cohort from the general population (96.6%; relative risk [RR] of death: 2.35; 95% CI: 1.70, 3.29; *P*<0.0001). A significantly increased mortality was notably seen among those aged 50 to <60 years old (RR: 18.0; 95% CI: 2.2, 148.2) and those aged 60 to <70 years old (RR: 4.1; 95% CI: 1.9, 8.7). While the asthmatic control cohort had a numerically higher survival probability at 2 years than the uncontrolled severe asthmatic cohort, the difference was not significant (94.3% vs 92.0%; *P*=0.0747). However, the analysis of mortality by age group showed a statistically significantly higher risk of mortality in patients aged 60 to <70 years (8% vs 2% deaths in uncontrolled severe asthmatic cohort vs asthmatic control cohort ; RR: 4.1; 95% CI: 1.2, 14.0; Figure S2, Supplementary File).

Figure 2 shows survival over time among the 3 cohorts. Compared with both control cohorts, the increased risk of mortality was observed early, and the difference increased during follow-up.

The Cox model for mortality risk showed a significant impact of a history of psychiatric diseases (Table S1, Supplementary File). In the category "without history of psychiatric diseases", the mortality risk increased significantly by an average of 3.25 in the uncontrolled severe asthmatic cohort compared to the general population cohort (hazard ratio [HR]: 3.25; 95% CI: 2.14, 4.92). Likewise, other comorbidities increased mortality risk in the uncontrolled severe asthmatic cohort, especially for cancer (HR: 2.40; 95% CI: 1.64, 3.50; Table S1).

Figure S3 shows that, among subjects without a history of psychiatric diseases, overall survival was lower in the uncontrolled severe asthmatic cohort compared to the general population, with a difference of 10% at 24 months.

Healthcare utilization

Table 1 shows the level of healthcare utilization for all 3 cohorts during follow-up. The proportion of patients requiring medical care in the hospital setting at least once during follow-up was significantly higher in the uncontrolled severe asthmatic population versus both control populations.

Table 1. Comparison of the results for mortality and main healthcare use per patient during the 2-year follow-up

	Cohort of uncontrolled severe asthmatics (N=739)	General population cohort (N=2,217)	*P*-Value	Asthmatic control cohort (n=739)	*P*-Value
Deaths, n (%)	**59 (8.0)**	**75 (3.4)**	***P*<0.0001**	**42 (5.7)**	***P*=0.0747**
Deaths by age group, n (%)					
<20	0 (0.0)	0 (0.0)		0 (0.0)	
20-<30	0 (0.0)	1 (1.3)		0 (0.0)	
30-<40	0 (0.0)	1 (1.3)		0 (0.0)	
40-<50	0 (0.0)	1 (1.3)	*P*=0.0393	0 (0.0)	*P*=0.0366
50-<60	6 (10.2)	1 (1.3)		1 (2.4)	
60-<70	15 (25.4)	11 (14.7)		3 (7.1)	
70-<80	14 (23.7)	16 (21.3)		10 (23.8)	
80-<90	15 (25.4)	20 (26.7)		16 (38.1)	
≥90	9 (15.3)	24 (32.0)		12 (28.6)	
Mean age at death (σ)	**76.1 (12.5)**	**79.7 (14.5)**	*P*=0.0266	83.0 (9.7)	
Min-max	51.0-102.0	25.0-100.0		55.0-102.0	*P*=0.0266
At least 1 medical care act done at hospital, n (%)	**478 (64.7)**	**774 (34.9)**	***P*<0.0001**	**408 (55.2)**	***P*=0.0002**
ED visit	318 (43.0)	465 (21.0)	*P*<0.0001	247 (33.4)	*P*=0.0002
All-cause hospitalization	409 (55.3)	556 (25.1)	*P*<0.0001	349 (47.2)	*P*=0.0023
Asthma-related hospitalizations (asthma and severe exacerbation)[a]	27 (3.7)	0 (0.0)	NA	12 (1.6)	*P*=0.0163
Asthma-related hospitalizations with at least 1 visit in intensive care unit	3 (0.4)	0 (0.0)	NA	1 (0.1)	0.3173
At least 1 medical visit during follow-up, n (%)	**708 (95.8)**	**1,995 (90.0)**	***P*<0.0001**	**709 (95.9)**	***P*=0.8981**
General practitioner	602 (81.5)	1,628 (73.4)	*P*<0.0001	620 (83.9)	*P*=0.2185
Respiratory specialist	94 (12.7)	53 (2.4)	*P*<0.0001	42 (5.7)	*P*<0.0001
Ear-nose-throat specialist	67 (9.1)	122 (5.5)	*P*<0.0001	37 (5.0)	*P*=0.0030
At least 1 paramedical visit during follow-up, n (%)	**600 (81.2)**	**1,390 (62.7)**	***P*<0.0001**	**546 (73.9)**	***P*=0.0011**
Nurse consultation	531 (71.9)	1,184 (53.4)	*P*<0.0001	496 (66.7)	*P*=0.0353
Physiotherapy consultation	320 (43.3)	673 (30.4)	*P*<0.0001	259 (35.0)	*P*=0.0013
At least 1 filled prescription for an asthma medication during follow-up, n (%)	**726 (98.2)**	**257 (11.6)**	***P*<0.0001**	**638 (86.3)**	***P*<0.0001**
Short-acting bronchodilator	606 (82.0)	100 (4.5)	*P*<0.0001	396 (53.6)	*P*<0.0001
Long-acting bronchodilator: LAMA/LABA	316 (42.8)	53 (2.4)	*P*=0.0004	190 (25.7)	*P*<0.0001
Long-acting bronchodilator: xanthines	56 (7.6)	2 (0.1)	*P*<0.0001	10 (1.4)	*P*<0.0001
Anti-inflammatory medication (ICS ± OCS)	506 (68.5)	115 (5.2)	*P*<0.0001	273 (36.9)	*P*<0.0001
Anti-inflammatory medication (ICS ± OCS) and long-acting bronchodilator	626 (84.7)	128 (5.8)	*P*<0.0001	413 (55.9)	*P*<0.0001

	Cohort of uncontrolled severe asthmatics (N=739)	General population cohort (N=2,217)	*P*-Value	Asthmatic control cohort (n=739)	*P*-Value
At least 1 visit to a GP, respiratory specialist, or allergy specialist, followed within 10 days by a filled prescription of OCS, n (%)	481 (65.1)	447 (20.2)	*P*<0.0001	229 (31.0)	*P*<0.0001
At least 1 filled prescription of a medication of interest during follow-up, n (%)	**727 (98.4)**	**1,847 (83.3)**	***P*<0.0001**	**678 (91.7)**	***P*<0.0001**
Intranasal antihistamines	22 (3.0)	13 (0.6)	*P*<0.0001	10 (1.4)	*P*=0.0339
Ocular antihistamines	43 (5.8)	80 (3.6)	*P*=0.0004	27 (3.7)	*P*=0.0523
Systemic antihistamines	488 (66.0)	675 (30.4)	*P*<0.0001	273 (36.9)	*P*<0.0001
Intranasal corticosteroids	420 (56.8)	567 (25.6)	*P*<0.0001	230 (31.1)	*P*<0.0001
Nonsteroidal anti-inflammatory drugs	407 (55.1)	1,083 (48.8)	*P*<0.0001	317 (42.9)	*P*<0.0001
Antibiotics	670 (90.7)	1,323 (59.7)	*P*<0.0001	501 (67.8)	*P*<0.0001
Proton-pump inhibitors	506 (68.5)	980 (44.2)	*P*<0.0001	348 (47.1)	*P*<0.0001
Psychotropic drugs	426 (57.6)	840 (37.9)	*P*<0.0001	320 (43.3)	*P*<0.0001
Topical corticosteroids	235 (31.8)	512 (23.1)	*P*<0.0001	145 (19.6)	*P*<0.0001
Topical immunosuppressants	2 (0.3%)	1 (0.0)	*P*=0.0588	0 (0.0%)	NA

[a] Excluding stays of less than 1 night (or Z codes).

Key: ED – emergency department; GP – general practitioner; ICS – inhaled corticosteroid; LABA – long-acting ß2-agonist; LAMA – long-acting muscarinic antagonist; NA – not applicable; OCS – oral corticosteroid.

A 2-fold increase in ED visits and all-cause or asthma-related hospitalizations was observed for uncontrolled severe asthmatic patients compared with the general population (64.7% vs 34.9%; *P*<0.0001). These patients also had a statistically significant increased use of other main components of care, such as medical visits (95.8% vs 90.0%; *P*<0.0001) and paramedical visits (81.2% vs 62.7%; *P*<0.0001). A statistically significant increase was also seen for the healthcare utilization comparison with the asthmatic cohort, where uncontrolled severe asthmatic patients also had more ED visits and hospitalizations (64.7% vs 55.2%; *P*=0.0002) and paramedical visits (81.2% vs 73.9%; *P*=0.0011).

For drug prescriptions, the proportion of patients receiving medications overall was higher in uncontrolled severe asthmatic patients compared to matched individuals from the general population cohort, both in terms of asthma-related treatments, inclusive of oral corticosteroid therapy (98.2% vs 11.6%; *P*<0.0001), and other treatments, such as antibiotics, nonsteroidal anti-inflammatory drugs, and psychotropic drugs (98.4% vs 83.3%; *P*<0.0001). Uncontrolled severe asthmatic patients also had significantly higher medication use than the asthmatic controls both for asthma-related treatments (98.2% vs 86.3%; *P*<0.0001) and other medications (98.4% vs 91.7%; *P*<0.0001).

Costs

Healthcare use increases translated into higher costs. Mean costs associated with healthcare utilization during the 2-year follow-up were significantly higher for uncontrolled severe asthmatic patients (€14,020) compared to the general population (€3,564; *P*<0.0001) or asthmatic controls (€6,418; *P*<0.0001), regardless of the expenditure (Table 2).

Table 2. Comparison of costs (reimbursement amounts, in Euros) associated with hospital and outpatient use, per patient, over a 2-year period after the index date (uncontrolled severe asthmatic patients vs general population and asthmatic control cohorts)

		Cohort of uncontrolled severe asthmatics (N=739)	General population cohort (N=2,217)	*P*-Value	Asthmatic control cohort (n=739)	*P*-Value
Hospitalization	Mean (σ)	8,163 (20,669)	1,800 (7,991)		3,529 (13,702)	
	Median	425.91(0.00-5,854)	0.00 (0.00-0.00)	*P*<0.0001	0.00 (0.00-1,284)	*P*<0.0001
	Min-max	0.00-246,483	0.00-176,423		0.00-190,456.80	
ED visit without hospitalization	Mean (σ)	12.47 (27.74)	6.16 (17.76)		9.49 (33.03)	
	Median (Q1-Q3)	0.00 (0.00-24.86)	0.00 (0.00-0.00)	*P*<0.0001	0.00 (0.00-0.00)	*P*<0.0001
	Min-max	0.00-319.21	0.00-273.42		0.00-671.13	
Medical visits	Mean (σ)	643.02 (1,068)	367.57 (437.39)		496.15 (657.70)	
	Median (Q1-Q3)	491.39 (278.42-785.97)	265.02 (113.30-498.51)	*P*<0.0001	376.35 (216.72-611.98)	*P*<0.0001
	Min-max	0.00-24,882	0.00-6,861		0.00-11,547	
Laboratory tests	Mean (σ)	240.95 (321.20)	153.74 (265.85)		203.48 (285.37)	
	Median (Q1-Q3)	145.14 (52.73-295.49)	85.23 (0.00-179.93)	*P*<0.0001	126.25 (54.32-236.76)	*P*=0.0131
	Min-max	0.00-3,137	0.00-5,727		0.00-2,461	
Paramedical visits	Mean (σ)	1,406 (4,827)	746.87 (2,986.03)		968.41 (3,236.10)	
	Median (Q1-Q3)	176.08 (11.98-689.00)	17.97 (0.00-288.02)	*P*<0.0001	42.48 (0.00-468.70)	*P*<0.0001
	Min-max	0.00-65,527	0.00-50,060		0.00-36,145	
Medications	Mean (σ)	3,076 (9,131.20)	199,49 (409,72)		721.35 (747.43)	
	Median (Q1-Q3)	1,525 (1,037-2,185)	58.38 (11,84-220,45)	*P*<0.0001	523.35 (246.07-957.22)	*P*<0.0001
	Min-max	0.00-95,453	0.00-5,855		0.00-9,472	
Total costs	**Mean (σ)**	**14,020 (24,076)**	**3,564 (9,540)**		**6,418 (15,109)**	
	Median (Q1-Q3)	**4,624.70 (2,492-13,897)**	**824.75 (297.00-2,286)**	***P*<0.0001**	**1,964.82 (1,020-4,906)**	***P*<0.0001**
	Min-max	**105.03-253,160**	**0.00-190,380**		**0.00-193,294**	

Key: ED – emergency department.

The average cost of an uncontrolled severe asthmatic patient who died was significantly higher than that of a surviving patient (€28,009 vs €11,850.60; *P*<0.0001). Primary drivers of this increase in uncontrolled severe asthmatic patients were hospitalizations (5-fold and 2-fold increases vs the general and asthmatic populations, respectively), drugs of interest (16-fold and 4-fold increases vs the general and asthmatic populations, respectively), and paramedical fees (2-fold and 1.4-fold increases vs the general and asthmatic populations, respectively).

DISCUSSION

Given the lack of recent data quantifying impact of uncontrolled severe asthma on public health, the RESONANCE study provided important data characterizing this population and comparing it to the general and asthmatic populations in terms of morbidity and mortality as well as healthcare use and associated costs. This is the first study to specifically compare uncontrolled severe asthmatic patients with the overall asthmatic population.

The clinical burden of uncontrolled severe asthma was demonstrated through the increased risk of mortality, use of additional treatments (asthma-related treatment and other associated treatments), and hospitalizations during the 2-year follow-up period in comparison with matched patients from the general and asthmatic populations. The average costs of uncontrolled severe asthma to the healthcare system during the 2 years of follow-up represented nearly 4 times that of matched patients from the general population over the same period (difference of €10,456 per patient). This amounts to an increase of 293% in costs—more than twice that of matched asthmatic controls—in whom an increase of 118% in costs was seen over 2 years (difference of €7,601 per patient with the general population). Bourdin et al found an incremental cost of $5,276 to the healthcare system annually when comparing severe asthmatic patients to the general population, although a 2-year extrapolation would be biased due to the non-annual rate of care seeking in the study population.[12] However, no specific assessment of uncontrolled severe asthma was performed.

Hospitalizations were the main driver of healthcare use and costs, in line with other studies assessing the economic burden of asthma.[4,7,14] Costs during follow-up could have been influenced by the cost of hospitalization occurring at index date, since it was part of the selection criteria, given its connection with asthma non-control; however, the influence of this phenomenon was limited, as only 5.1% of patients were selected based solely on this criterion.

An important finding highlighted by this study is that the cost of uncontrolled severe asthma was partly explained by healthcare received by patients who ended up by dying during follow-

up, emphasizing the importance of healthcare expenses during the last months or years of life in this population.

Our study also assessed the size of the uncontrolled severe patient population. The 739 patients identified among the total population of 16,588 asthmatic patients suggest that this small but high-risk population represents 4.5% of all asthmatic patients in France in 2014. When extrapolating to the entire adolescent and adult French population, this represents a prevalence of 0.15% (i.e., 86,342 patients; 95% CI: 80,341, 92,789), which is slightly lower than other severe asthma populational estimates that used different definitions of asthma severity and did not account for asthma non-control.[12,15]

The uncontrolled severe asthmatic population was identified by means of a comprehensive algorithm, where great care was placed in the definitions of asthma, severity, and control to ensure the accuracy of the cohorts and palliate the lack of clinical data and use of a single marker, allowing identification of this unique population. Asthma was defined with robust data, such as asthma-related hospitalizations and complications, asthma-related full coverage for a long-term condition (ALD), and specific treatments.

Two cohorts were compared to uncontrolled severe asthmatic patients. The objective of the general population control cohort was to highlight the absolute burden of uncontrolled severe asthma in the population. Matching on key sociodemographic characteristics aimed to control for potential confounding bias and ensure comparability of the populations, which was confirmed by standardized differences. In addition, a Cox regression model was developed post-hoc to compare mortality risk between the uncontrolled severe asthmatic cohort and the general population; as expected, the 24-month survival was lower in the uncontrolled severe asthma cohort.

The asthmatic control cohort was selected and matched to uncontrolled severe asthmatic patients using propensity scores to control potential confounding factors using all available and relevant variables. Given that this control population includes severe but controlled or

non-controlled but non-severe asthmatics, it is not a population exclusively comprising low-risk patients.

The study was conducted using the EGB, a well-recognized and robust populational medical administrative database that confers many advantages, such as the completeness of mortality data and comprehensiveness of healthcare reimbursed for all patients. Of note, the EGB does not include clinical information such as visit reason, diagnoses made outside hospitals, biological test results, or patients' anthropometric data.

The challenges associated with the use of administrative databases have been well documented;[16] in this study, the difficulties in selecting the population of uncontrolled severe asthmatics were associated with a potential for measurement bias related to coding errors in hospital diagnoses; this source of error is likely limited and non-differential between groups. The algorithms assumed that filled prescriptions were proxies to treatment use; however, it is not possible to confirm that a filled prescription has been taken.

Potential indications of asthma treatments for other conditions, such as COPD, were accounted for as part of patient selection by adding exclusion criteria. Despite this, some COPD patients also suffering from asthma may have been included given the average age of the asthmatic cohorts. It is anticipated that the criteria requiring continuous insurance coverage may have resulted in a lower number of younger patients being included due to student-specific insurance offered during school years; however, the impact of this limitation on the results is likely minimal.

The EGB offers the advantage of a limited number of patients lost to follow-up given the universal healthcare system present in France. It also has a few limitations: while most patients were covered by the general scheme, patients covered by other plans may not have been selected due to the later integration of those plans in the EGB. Also, the algorithm used to define asthma and index date excluded patients who died at the hospital around the time of

the index date, thereby potentially excluding the most severe and uncontrolled patients. Finally, additional residual confounding factors may persist despite the matching process.

This large study, which is the first allowing the comparison between uncontrolled severe asthmatic patients and other asthmatic patients and the general population, highlighted that severe asthma associated with non-control significantly affects mortality, healthcare use, and associated costs. This emphasized that close attention should be paid to ensure appropriate management of severe asthmatic patients and monitoring of the level of control of asthma symptoms.

CONCLUSIONS

This database study demonstrates the huge burden of uncontrolled severe asthma in terms of mortality, morbidity, and healthcare resource consumption compared to other patients with asthma and the general population. These findings emphasize the importance of appropriate management in this high-risk population.

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Contributors All authors participated in the interpretation of the data, provided critical feedback and final approval for submission, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses. Stève Bénard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: all authors
Acquisition, analysis, or interpretation of data: all authors
Drafting of the manuscript: de Larrard and Bénard
Critical revision of the manuscript for important intellectual content: Roche, Demoly, Garcia, Cancalon, Perez, Mahieu and Vieu
Statistical analysis: de Larrard, Bénard and Cancalon
Administrative, technical, or material support: Bénard, Perez, Mahieu and Vieu
Supervision: all authors

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Competing interests Pr Pascal Demoly has received honoraria and/or research grants from ALK, Mylan-Viatris, Stallergènes, ThermoFisher Scientific, AstraZeneca, GSK, Novartis, Ménarini, and Regeneron.
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Laurine Vieu, Aymeric Mahieu, Vincent Perez are Sanofi employee and may hold shares and/or stock options in the company.

Patient consent for publication Not required.

Data Availability Statement No additional data available.

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LIST OF FIGURE TITLES AND LEGENDS

FIGURE 1. RESONANCE study design

FIGURE 2. 24-month survival for the uncontrolled severe asthmatic cohort vs general population and asthmatic control cohorts

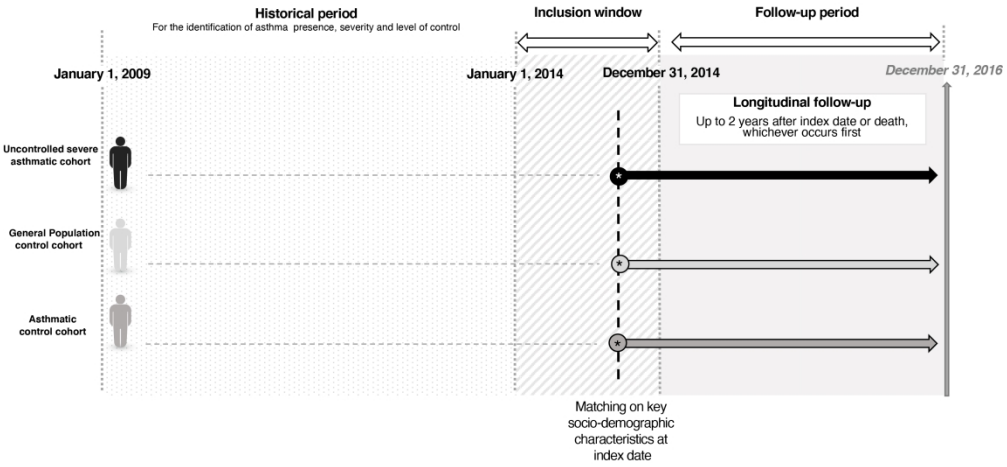

FIGURE 1. RESONANCE study design

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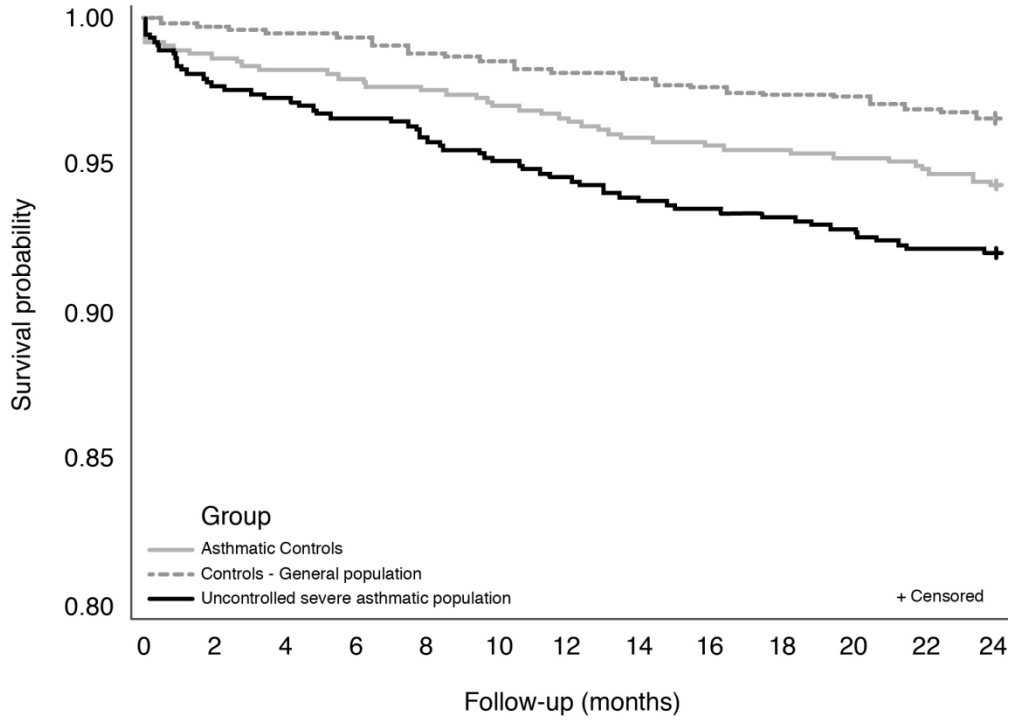


FIGURE 2. 24-month survival for the uncontrolled severe asthmatic cohort vs. general population and asthmatic control cohorts

166x119mm (300 x 300 DPI)

Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: the RESONANCE study

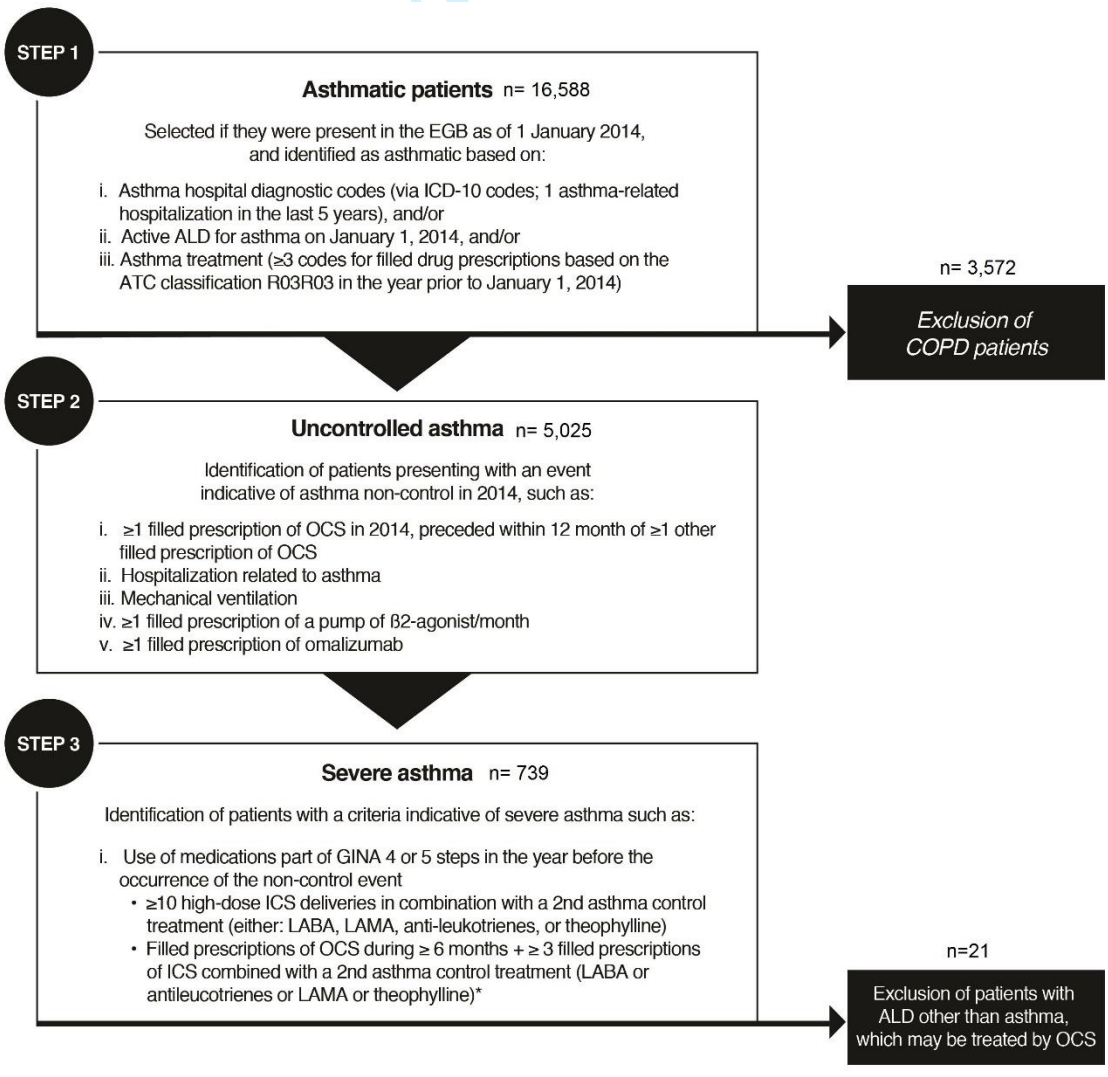
Nicolas Roche[1], Gilles Garcia[2], Alexandre de Larrard[3], Charlotte Cancalon[3], Stève Bénard[3], Vincent Perez[4], Aymeric Mahieu[4], Laurine Vieu[4], Pascal Demoly[5]

Supplementary materials

FIGURE S1. Patient selection algorithm

Key: ALD – affection de longue durée (long-term condition); ATC – Anatomical Therapeutic Chemical; COPD – chronic obstructive pulmonary disease; ICD-10 – International Classification of Diseases, 10th Revision; ICS – inhaled corticosteroid; LABA – long-acting ß2-agonist; LAMA – long-acting muscarinic antagonist; OCS – oral corticosteroid.

Footnote:
* Of note, these criteria did not apply to patients with an ALD other than asthma (ie, rheumatoid arthritis, ulcerative colitis, Crohn's disease, cancer, etc) who can be treated by OCS identified by an exploratory analysis of ALD of patients from the target population meeting criterion.



Methods – Additional details on drugs of interest

Asthma treatments:

- short-acting beta2-agonists (SABA),
- long-acting beta2-agonists (LABA),
- long-acting anticholinergics (LAMA),
- antileukotriene receptor antagonists (LTRA),
- xanthines,
- inhaled and oral corticosteroids (ICS and OCS),
- combination treatments.

Other drug classes of interest:

- nasal antihistamines,
- antihistamines,
- nonsteroidal anti-inflammatory drugs (NSAIDs),
- antibiotics,
- proton pump inhibitors (PPIs),
- psychotropic drugs,
- topical corticosteroids,
- topical immunosuppressants.

Methods – ICD-10 codes used

For the Asthma definition

J45.0 Predominantly allergic asthma
J45.1 Non-allergic asthma
J45.8 Mixed asthma
J45.9 Asthma, Unspecified
J46 Status asthmaticus
J96 Respiratory failure, not elsewhere classified

For the COPD definition

J41 Simple and mucopurulent chronic bronchitis
J42 Unspecified chronic bronchitis
J43 Emphysema
J44 Other chronic obstructive pulmonary disease
J47 Bronchiectasis
J61 Pneumoconiosis due to asbestos and other mineral fiber
J62.8 Pneumoconiosis due to other dust containing silica
J68.0 Bronchitis due to chemicals, gases, fumes and vapors
E84 Mucoviscidosis
J92.0 Pleural plaque with presence of asbestos
J94.8 Other specified pleural conditions
J96.1+0 Insuffisance respiratoire chronique obstructive

Methods – Variables defined for matching

1. nasal corticosteroid (Yes/No)
2. systemic antihistamine (Yes/No)
3. non-steroidal anti-inflammatory drugs (Yes/No)
4. antibiotic (Yes/No)
5. proton pump inhibitor (Yes/No)
6. dermocorticoids (Yes/No)
7. psychotropic drug (Yes/No)
8. age (years)
9. number of outpatient consultations
10. charlson's score
11. consultation with a nurse (Yes/No)
12. cardio-vascular diseases (Yes/No)
13. ocular antihistamine (Yes/No)
14. hypertension (Yes/No)
15. osteoporosis (Yes/No)
16. number of consultations with a physiotherapist
17. consultations with a physiotherapist (Yes/No)
18. depression (Yes/No)
19. psychiatric illness (Yes/No)
20. number of emergency room visits
21. hospitalisation (Yes/No)
22. number of consultations with a nurse
23. emergency room visits (Yes/No)
24. number of hospitalizations
25. nasal antihistamine (Yes/No)
26. cataract (Yes/No)
27. nasal polyposis (Yes/No)
28. number of hospital consultations
29. gastroesophageal reflux (Yes/No)
30. dyslipidemia (Yes/No)
31. arrhythmia (Yes/No)
32. hospital consultations (Yes/No)
33. cerebrovascular diseases (Yes/No)
34. anxiety (Yes/No)
35. rhinosinusitis (Yes/No)
36. heart failure (Yes/No)
37. diabetes (Yes/No)
38. coronary heart disease (Yes/No)
39. sex
40. psychotic disorders (Yes/No)
41. outpatient consultation (Yes/No)
42. topical immunosuppressant (Yes/No)
43. CMU (Yes/No)
44. myocardial infarction (Yes/No)
45. atopic dermatitis (Yes/No)

FIGURE S2. Analysis of mortality by age group

Age group	Target population	Deceased target population	Asthmatic control cohort	Deceased asthmatic control cohort	RR	95% CI	RRR
[50;60[	140	6	135	1	5,79	[0,71;47,41]	-4,79
[60;70[	183	15	151	3	4,13	[1,22;13,97]	-3,13
[70;80[	136	14	161	10	1,66	[0,76;3,60]	-0,66
[80;90[	86	15	117	16	1,28	[0,68;2,41]	-0,28
≥90	28	9	21	12	0,56	[0,40;0,79]	0,44

Target population: Uncontrolled severe asthmatic cohort

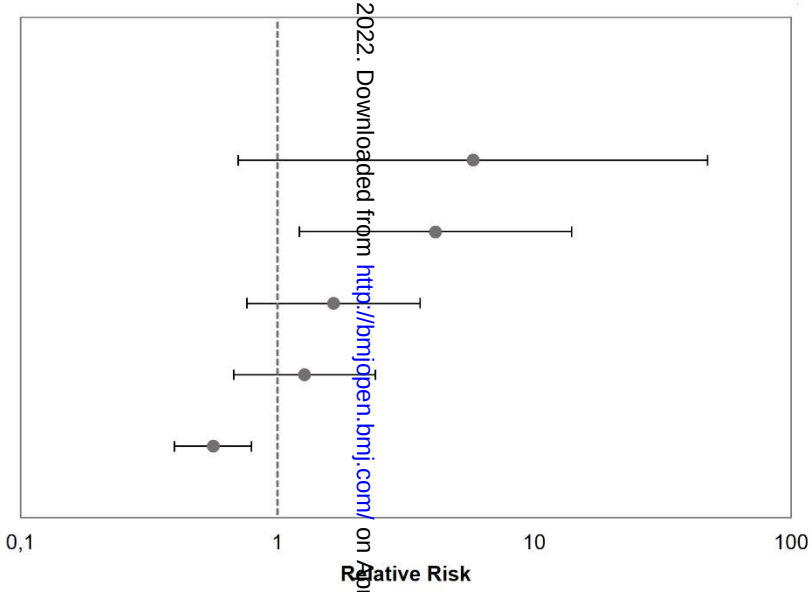
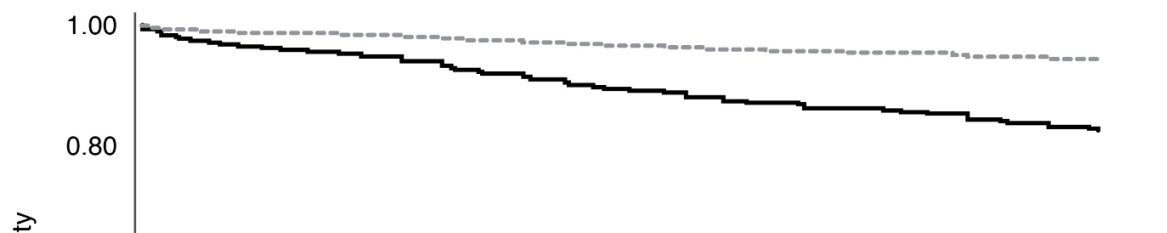


Table S1. Results of multivariate Cox model among uncontrolled severe asthmatic cohort and controls of general population

Covariate	Hazard ratio	95% CI
Population with history of psychiatric diseases (target population vs controls of general population)	1.224	0.663, 2.260
Population without history of psychiatric diseases (target population vs controls of general population)	3.246	2.140, 4.922
Age (1-year increase)	1.068	1.052, 1.085
History of cardiovascular diseases (with vs without)	1.911	1.181, 3.092
History of diabetes (with vs without)	1.661	1.110, 2.485
History of psychiatric diseases: Target population (with vs without)	0.927	0.521, 1.649
History of psychiatric diseases: Controls of general population (with vs without)	2.457	1.541, 3.916
Cancer comorbidity of the Charlson score (with vs without)	2.395	1.639, 3.500

Key: CI – confidence interval.

FIGURE S3. 24-month survival for the uncontrolled severe asthmatic cohort versus general population among subjects without history of psychiatric disease



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7 (Figure S1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: findings from the retrospective observational RESONANCE study in France

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Health economics, Epidemiology
Keywords:	Asthma < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, HEALTH ECONOMICS

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Word Count: 3,414 words

Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: findings from the retrospective observational RESONANCE study in France

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ABSTRACT

Word Count: 300

Objective: To characterize uncontrolled severe asthma and compare the disease burden with the general and asthmatic populations.

Design: Retrospective observational study using a national sample of a French healthcare database (*Echantillon Généraliste des Bénéficiaires [EGB])*.

Setting: The EGB, an anonymized permanent sample of health insurance databases, representing 1/97th of the French population.

Participants: Patients (≥12 years) were selected in year 2014 and followed 2 years. A cohort of patients with uncontrolled severe asthma was defined using an algorithm based on peer-reviewed literature and Global Initiative for Asthma recommendations. Index date was the occurrence of the first marker of uncontrolled asthma. This cohort was matched with 2 control cohorts, general population and asthmatic controls, on baseline characteristics.

Main outcomes measures: Mortality, healthcare use, and associated costs were studied in the 2 years of follow-up.

Results: Among 467,716 individuals in the EGB, 16,588 patients with asthma were identified, including 739 (4.5%) with uncontrolled severe disease. The survival probability at 2 years for patients with uncontrolled severe asthma (92.0%) was lower than in the general population cohort (96.6%; relative risk of death: 2.35; 95% confidence interval: 1.70-3.29; *P*<0.0001) and tended to be lower than in the control asthmatic cohort (94.3%; *P*=0.07). Emergency department visits and hospitalizations were higher in patients with uncontrolled severe asthma than in the general population (64.7% *vs.* 34.9%; *P*<0.0001) and asthmatic controls (64.7% *vs.* 55.2%; *P*=0.0002). Other components of healthcare use (medical and paramedical visits, medications) were increased in patients with uncontrolled severe asthma compared with control populations. These increases translated into higher costs (*P*<0.0001 for both comparisons).

Conclusions: This study demonstrates the huge burden of uncontrolled severe asthma in terms of mortality, morbidity, and healthcare resource consumption compared to other patients with asthma and the general population, and emphasizes the importance of appropriate management in this high-risk population.

Strengths and limitations of this study:

- The study was conducted using a well-recognized and robust populational medical administrative database that confers many advantages, such as the completeness of mortality data and comprehensiveness of healthcare reimbursed for all patients.
- This is the first study to specifically compare patients with uncontrolled severe asthma with the overall asthmatic population.
- Comparability of studied groups was ensured by careful matching process.
- The lack of clinical data was mitigated by the use of a comprehensive algorithm to identify the uncontrolled severe asthmatic population with great care in the definitions of asthma, severity, and control to ensure the accuracy of the cohorts.
- The criteria requiring continuous insurance coverage may have resulted in a marginally lower number of younger patients being included due to student-specific insurance offered during school years.

INTRODUCTION

Asthma is one of the most common chronic diseases and is a major cause of morbidity. This heterogeneous disease is characterized by its chronic inflammatory nature which can lead to airway remodeling and presents with varied levels of severity and control. While a majority of patients with asthma have mild to moderate disease according to Global Initiative for Asthma (GINA) criteria, between 3% and 10% present a severe asthma, which may be life-threatening, particularly due to severe and potentially fatal exacerbations.[1,2] Despite implementation of an optimal management strategy, many patients with severe asthma are not able to achieve disease control, leading to poor quality of life and significant social and health burdens. Asthma therefore represents an important public health issue given its impact on work productivity (*i.e.*, absenteeism and presenteeism) and the costs associated with disease management and healthcare resource utilization.[3–7]

In the context of the rapidly evolving landscape of expensive GINA step 5 asthma treatments, it is crucial to generate up-to-date data on the real-life population burden of uncontrolled severe asthma in adolescents and adults and to understand the relative impact of the disease in patients with severe asthma compared to the general and to non-severe asthmatic populations. The framework of the French Health Data Hub project provided the opportunity to access the public medico-administrative database to address this specific issue.

The RESONANCE study was undertaken to: (1) characterize uncontrolled severe asthma in patients aged 12 years and older, and (2) compare the disease burden in terms of mortality, healthcare utilization, and associated costs within this population to two series of matched controls from the general population and the asthmatic population (*i.e.* total asthmatic population excluding those with uncontrolled severe asthma).

METHODS

Study Design

A retrospective, non-interventional cohort study was carried out using a large populational database from France, the *Echantillon Généraliste des Bénéficiaires* (EGB). All individuals aged 12 years and over in the EGB were included in the source population. A cohort of adolescent and adult patients who had uncontrolled severe asthma during 2014 were identified. Their index date was the date of the first event identifying non-control during 2014. Two control cohorts were defined, one from the general population and another of patients with asthma. For each control selected, the index date assigned was the calendar index date of respective matched patients from the uncontrolled severe asthma cohort.

Historical information on comorbidities, healthcare use, and treatments received were collected up to five years preceding the index date to assess baseline characteristics. Socio-demographic characteristics were collected at index date for the three cohorts. Cohorts were followed up to two years after the index date or death, whichever occurs first, to assess the outcomes of interest (Figure 1).

Data sources

The EGB is an anonymized permanent sample of health insurance databases representing 1/97th of the entire French population.[8,9] Given the universal healthcare system in France, the EGB is a sizeable and representative sample of all subjects covered by various social security schemes and now includes nearly 660,000 beneficiaries.

The EGB contains information on demographics (age, sex, area of residence, etc.); outpatient care reimbursement (including drug dispensing); medical care and reimbursement received in outpatient and hospital settings; specific information on the right to universal supplementary health coverage (CMU-c); whether beneficiaries are affected by a long-term condition (*affection de longue durée*; ALD); and the date of death. The database benefits from the

interlinkage of several administrative data sources, thereby allowing an assessment of beneficiaries' healthcare utilization over time.

Subjects

Patients with uncontrolled severe asthma were identified using an algorithm based on events occurring in 2014 (Figure S1, Supplementary File). This algorithm was designed following a literature review,[10–12] and GINA management recommendations,[13] in collaboration with an expert scientific committee composed of 3 respiratory specialists.

Patients with evidence of another chronic pulmonary disease, including chronic obstructive pulmonary disease (COPD), identified through International Classification of Diseases, 10th Revision (ICD-10) or ALD codes, were excluded (see Supplementary File).

General population controls were randomly selected among all individuals, besides patients with uncontrolled severe asthma, present in the EGB in 2014. Controls were eligible to be matched with patients in the uncontrolled severe asthma cohort if they had the same age, sex, and CMU-c status at index date. Up to 3 controls per case were selected. Direct matching quality was assessed by comparing standardized differences between both cohorts (See Table S1, Supplementary File).

Individuals in the asthma cohort were randomly selected within the total asthmatic population present in the EGB in 2014, excluding those with uncontrolled severe asthma. Individuals were matched with patients in the uncontrolled severe asthma cohort on a 1:1 ratio using nearest neighbour propensity score matching. Propensity scores incorporating 45 variables recommended by the expert scientific committee, including sociodemographic characteristics, comorbidities, and history of healthcare use prior to index date. Standardized differences were used to assess matching quality (See Table S2, Supplementary File).

Collected data and outcomes

The following sociodemographic and clinical characteristics were considered:

- Up to 5 years prior to index date: comorbidities, treatments received, healthcare utilization (medical visits, emergency department [ED] visits, hospitalizations)
- At index date: age, sex, CMU-c status
- During follow-up:
    - Date of death, if applicable
    - Drugs of interest: asthma treatments and other classes of interest (see Supplementary File)
    - Healthcare utilization: Medical and paramedical visits (general medicine, respiratory specialists, otolaryngology, nursing support, physiotherapy), ED visits, and hospitalizations (all-cause and asthma-related)
    - Direct medical costs associated with medications and healthcare use (outpatient and hospital settings)

The primary objective of this study was to assess the number and proportion of patients with uncontrolled severe asthma aged 12 and older. Sociodemographic and clinical characteristics were provided for this population.

The secondary objective was to assess all-cause mortality and survival probability, healthcare use and associated costs in the 2 years after index date in the uncontrolled severe asthma cohort compared to the two matched control cohorts (general population and asthmatic controls).

Statistical analyses

Continuous variables were described using means, standard deviations, medians, and ranges, whilst categorical variables were described as frequencies.

Crude cumulative all-cause mortality rates at 2 years were obtained for all cohorts using the Kaplan-Meier methodology, whereby the probability of survival from index date through follow-up was estimated. The comparative analyses of mortality, healthcare utilization, and

associated costs between the primary cohort and matched controls were conducted using paired Student's *t*-tests or Wilcoxon signed-rank tests for quantitative variables according to their distribution, and Mc Nemar tests for qualitative variables. A post-hoc analysis using a Cox regression model was built to compare mortality between the uncontrolled severe asthmatic cohort and general population. The final model included the following variables: population (uncontrolled severe asthmatic cohort *vs*. general population), age, history of cardiovascular disease, diabetes, psychiatric disease, and cancer. Interactions between the variable "population" and other covariates included in the model were tested. Interaction between population and history of psychiatric disease was significant and was thus included in the final model. Costs were evaluated from the collective perspective, and all costs were reevaluated with adjustment to 2018 Euros (€) using a consumer price index (health data index 4011-E, published by national institute of statistics and economic studies, *Institut National de la Statistique et des Études Économiques*, *INSEE*), since 2018 was the date of data access. All analyses were performed using the SAS 9.4 software package (SAS Institute, Cary, NC, USA).

Ethical considerations

The data considered as part of this study were anonymized to ensure confidentiality at the patient level. Data handling, processing, and analysis were carried out in alignment and with authorizations from an independent committee (*CEREES, Comité d'Expertise pour les Recherches, les Études et les Évaluations dans le domaine de la Santé*; favorable opinion on June 14, 2018; TPS 31996) and from the French National Data Protection Agency *(CNIL, Commission Nationale de l'Informatique et des Libertés*; Authorization DR-2018-097).

Patient and Public Involvement Statement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Population selection

Of the 467,716 adolescents and adults present in the EGB, a total of 16,588 patients with asthma were identified and 5,025 of these exhibited a marker of uncontrolled disease in 2014 (Figure S1, Supplementary File). Among these, 739 patients with uncontrolled severe asthma were identified (57% female; mean age: 62.0 years; 10.0% with CMU-c, Tables S1 and S2, Supplementary File).

A total of 2,217 matched individuals were selected to build the control cohort from the general population (Table S1, Supplementary File). The control asthmatic population (all patients with asthma excluding those with uncontrolled severe asthma) included 739 patients matched to patients with uncontrolled severe asthma using propensity scores (53.0% women; mean age: 63.2 years; 7.7% with CMU-c, Table S2, Supplementary File). The majority of the 45 variables defined for matching were successfully balanced (Table S2 and Figure S2,Supplementary File).

Mortality

In total, 59 patients with uncontrolled severe asthma died in the 2-year follow-up period. The probability of survival at 2 years in this cohort was 92.0%, which is statistically significantly lower than that observed in the matched control cohort from the general population (96.6%; relative risk [RR] of death: 2.35; 95% CI: 1.70, 3.29; *P*<0.0001). A significantly increased mortality was notably seen among those aged 50 to <60 years old (RR: 18.0; 95% CI: 2.2, 148.2) and those aged 60 to <70 years old (RR: 4.1; 95% CI: 1.9, 8.7). While the asthmatic control cohort had a numerically higher survival probability at 2 years than the uncontrolled severe asthmatic cohort, the difference was not significant (94.3% *vs.* 92.0%; *P*=0.0747). However, the analysis of mortality by age group showed a statistically significantly higher risk of mortality in patients aged 60 to <70 years (8% *vs*. 2% deaths in uncontrolled severe asthmatic cohort *vs.* asthmatic control cohort; RR: 4.1; 95% CI: 1.2, 14.0; Figure S3, Supplementary File).

Figure 2 shows survival over time among the 3 cohorts. Compared with both control cohorts, the increased risk of mortality in uncontrolled severe asthma cohort was observed early, and became higher during follow-up.

The Cox model showed a significant impact of uncontrolled severe asthma compared to general population for mortality risk ($p<0.0001$). Other comorbidities (age, history of cardiovascular disease, diabetes, and cancer) increased mortality risk, especially cancer (hazard ratio [HR]: 2.40; 95% CI: 1.64, 3.50; Table S3, Supplementary File). Due to a significant interaction between population and history of psychiatric disease, effect of population was assessed by history of psychiatric disease (Table S3, Supplementary File). In patients without history of psychiatric disease, the mortality risk increased significantly by an average of 3.25 in the uncontrolled severe asthmatic cohort compared to the general population cohort (HR: 3.25; 95% CI: 2.14, 4.92).The difference in mortality risk was not significant in patients with history of psychiatric disease (HR: 1.22; 95% CI: 0.66, 2.26). Figure S4 shows that, among subjects without history of psychiatric disease, overall survival was lower in the uncontrolled severe asthmatic cohort compared to the general population, with a difference of 10% at 24 months.

Healthcare utilization

Table 1 shows the level of healthcare utilization for all three cohorts during follow-up. The proportion of patients requiring medical care in the hospital setting at least once during follow-up was significantly higher in the uncontrolled severe asthmatic population versus both control populations.

Table 1. Comparison of the results for mortality and main healthcare use per patient during the 2-year follow-up

	Cohort of uncontrolled severe asthmatics (N=739)	General population cohort (N=2,217)	*P*-Value	Asthmatic control cohort (n=739)	*P*-Value
Deaths, n (%)	**59 (8.0)**	**75 (3.4)**	***P*<0.0001**	**42 (5.7)**	***P*=0.0747**
Deaths by age group, n (%)					
<20	0 (0.0)	0 (0.0)		0 (0.0)	
20-<30	0 (0.0)	1 (1.3)		0 (0.0)	
30-<40	0 (0.0)	1 (1.3)		0 (0.0)	
40-<50	0 (0.0)	1 (1.3)	*P*=0.0393	0 (0.0)	*P*=0.0366
50-<60	6 (10.2)	1 (1.3)		1 (2.4)	
60-<70	15 (25.4)	11 (14.7)		3 (7.1)	
70-<80	14 (23.7)	16 (21.3)		10 (23.8)	
80-<90	15 (25.4)	20 (26.7)		16 (38.1)	
≥90	9 (15.3)	24 (32.0)		12 (28.6)	
Mean age at death (σ)	**76.1 (12.5)**	**79.7 (14.5)**	*P*=0.0266	83.0 (9.7)	
Min-max	51.0-102.0	25.0-100.0		55.0-102.0	*P*=0.0266
At least 1 medical care act done at hospital, n (%)	**478 (64.7)**	**774 (34.9)**	***P*<0.0001**	**408 (55.2)**	***P*=0.0002**
ED visit	318 (43.0)	465 (21.0)	*P*<0.0001	247 (33.4)	*P*=0.0002
All-cause hospitalization	409 (55.3)	556 (25.1)	*P*<0.0001	349 (47.2)	*P*=0.0023
Asthma-related hospitalizations (asthma and severe exacerbation)[a]	27 (3.7)	0 (0.0)	NA	12 (1.6)	*P*=0.0163
Asthma-related hospitalizations with at least 1 visit in intensive care unit	3 (0.4)	0 (0.0)	NA	1 (0.1)	0.3173
At least 1 medical visit during follow-up, n (%)	**708 (95.8)**	**1,995 (90.0)**	***P*<0.0001**	**709 (95.9)**	***P*=0.8981**
General practitioner	602 (81.5)	1,628 (73.4)	*P*<0.0001	620 (83.9)	*P*=0.2185
Respiratory specialist	94 (12.7)	53 (2.4)	*P*<0.0001	42 (5.7)	*P*<0.0001
Ear-nose-throat specialist	67 (9.1)	122 (5.5)	*P*<0.0001	37 (5.0)	*P*=0.0030
At least 1 paramedical visit during follow-up, n (%)	**600 (81.2)**	**1,390 (62.7)**	***P*<0.0001**	**546 (73.9)**	***P*=0.0011**
Nurse consultation	531 (71.9)	1,184 (53.4)	*P*<0.0001	496 (66.7)	*P*=0.0353
Physiotherapy consultation	320 (43.3)	673 (30.4)	*P*<0.0001	259 (35.0)	*P*=0.0013
At least 1 filled prescription for an asthma medication during follow-up, n (%)	**726 (98.2)**	**257 (11.6)**	***P*<0.0001**	**638 (86.3)**	***P*<0.0001**
Short-acting bronchodilator	606 (82.0)	100 (4.5)	*P*<0.0001	396 (53.6)	*P*<0.0001
Long-acting bronchodilator: LAMA/LABA	316 (42.8)	53 (2.4)	*P*=0.0004	190 (25.7)	*P*<0.0001
Long-acting bronchodilator: xanthines	56 (7.6)	2 (0.1)	*P*<0.0001	10 (1.4)	*P*<0.0001
Anti-inflammatory medication (ICS ± OCS)	506 (68.5)	115 (5.2)	*P*<0.0001	273 (36.9)	*P*<0.0001
Anti-inflammatory medication (ICS ± OCS) and long-acting bronchodilator	626 (84.7)	128 (5.8)	*P*<0.0001	413 (55.9)	*P*<0.0001

	Cohort of uncontrolled severe asthmatics (N=739)	General population cohort (N=2,217)	*P*-Value	Asthmatic control cohort (n=739)	*P*-Value
At least 1 visit to a GP, respiratory specialist, or allergy specialist, followed within 10 days by a filled prescription of OCS, n (%)	481 (65.1)	447 (20.2)	*P*<0.0001	229 (31.0)	*P*<0.0001
At least 1 filled prescription of a medication of interest during follow-up, n (%)	**727 (98.4)**	**1,847 (83.3)**	***P*<0.0001**	**678 (91.7)**	***P*<0.0001**
Intranasal antihistamines	22 (3.0)	13 (0.6)	*P*<0.0001	10 (1.4)	*P*=0.0339
Ocular antihistamines	43 (5.8)	80 (3.6)	*P*=0.0004	27 (3.7)	*P*=0.0523
Systemic antihistamines	488 (66.0)	675 (30.4)	*P*<0.0001	273 (36.9)	*P*<0.0001
Intranasal corticosteroids	420 (56.8)	567 (25.6)	*P*<0.0001	230 (31.1)	*P*<0.0001
Nonsteroidal anti-inflammatory drugs	407 (55.1)	1,083 (48.8)	*P*<0.0001	317 (42.9)	*P*<0.0001
Antibiotics	670 (90.7)	1,323 (59.7)	*P*<0.0001	501 (67.8)	*P*<0.0001
Proton-pump inhibitors	506 (68.5)	980 (44.2)	*P*<0.0001	348 (47.1)	*P*<0.0001
Psychotropic drugs	426 (57.6)	840 (37.9)	*P*<0.0001	320 (43.3)	*P*<0.0001
Topical corticosteroids	235 (31.8)	512 (23.1)	*P*<0.0001	145 (19.6)	*P*<0.0001
Topical immunosuppressants	2 (0.3%)	1 (0.0)	*P*=0.0588	0 (0.0%)	NA

[a] Excluding stays of less than 1 night (or Z codes).

Key: ED – emergency department; GP – general practitioner; ICS – inhaled corticosteroid; LABA – long-acting ß2-agonist; LAMA – long-acting muscarinic antagonist; NA – not applicable; OCS – oral corticosteroid.

A 2-fold increase in ED visits and all-cause or asthma-related hospitalizations was observed for patients with uncontrolled severe asthma compared with the general population (64.7% *vs.* 34.9%; *P*<0.0001). These patients also had a statistically significant increased use of other main components of care, such as medical visits (95.8% *vs*. 90.0%; *P*<0.0001) and paramedical visits (81.2% *vs*. 62.7%; *P*<0.0001). A statistically significant increase was also seen for the healthcare utilization comparison with the asthmatic cohort, where patients with uncontrolled severe asthma also had more ED visits and hospitalizations (64.7% *vs*. 55.2%; *P*=0.0002) and paramedical visits (81.2% *vs*. 73.9%; *P*=0.0011).

For drug prescriptions, the proportion of patients receiving medications overall was higher in patients with uncontrolled severe asthma compared to matched individuals from the general population cohort, both in terms of asthma-related treatments, inclusive of oral corticosteroid therapy (98.2% *vs*. 11.6%; *P*<0.0001), and other treatments, such as antibiotics, nonsteroidal anti-inflammatory drugs, and psychotropic drugs (98.4% *vs*. 83.3%; *P*<0.0001). Patients with uncontrolled severe asthma also had significantly higher medication use than the asthmatic controls both for asthma-related treatments (98.2% *vs*. 86.3%; *P*<0.0001) and other medications (98.4% *vs*. 91.7%; *P*<0.0001).

Costs

Healthcare use increases translated into higher costs. Mean costs associated with healthcare utilization during the 2-year follow-up were significantly higher for patients with uncontrolled severe asthma (€14,020) compared to the general population (€3,564; *P*<0.0001) or asthmatic controls (€6,418; *P*<0.0001), regardless of the expenditure (Table 2).

Table 2. Comparison of costs (reimbursement amounts, in Euros) associated with hospital and outpatient use, per patient, over a 2-year period after the index date (patients with uncontrolled severe asthma *vs.* general population and asthmatic control cohorts)

		Cohort of patients with uncontrolled severe asthma (N=739)	General population cohort (N=2,217)	*P*-Value	Asthmatic control cohort (n=739)	*P*-Value
Hospitalization	Mean (σ)	8,163 (20,669)	1,800 (7,991)		3,589 (13,702)	
	Median	425.91(0.00-5,854)	0.00 (0.00-0.00)	*P*<0.0001	0.00 (0.00-1,284)	*P*<0.0001
	Min-max	0.00-246,483	0.00-176,423		0.00-190,456.80	
ED visit without hospitalization	Mean (σ)	12.47 (27.74)	6.16 (17.76)		9.46 (33.03)	
	Median (Q1-Q3)	0.00 (0.00-24.86)	0.00 (0.00-0.00)	*P*<0.0001	0.00 (0.00-0.00)	*P*<0.0001
	Min-max	0.00-319.21	0.00-273.42		0.00-671.13	
Medical visits	Mean (σ)	643.02 (1,068)	367.57 (437.39)		496.15 (657.70)	
	Median (Q1-Q3)	491.39 (278.42-785.97)	265.02 (113.30-498.51)	*P*<0.0001	376.35 (216.72-611.98)	*P*<0.0001
	Min-max	0.00-24,882	0.00-6,861		0.00-11,547	
Laboratory tests	Mean (σ)	240.95 (321.20)	153.74 (265.85)		203.48 (285.37)	
	Median (Q1-Q3)	145.14 (52.73-295.49)	85.23 (0.00-179.93)	*P*<0.0001	126.25 (54.32-236.76)	*P*=0.0131
	Min-max	0.00-3,137	0.00-5,727		0.00-2,461	
Paramedical visits	Mean (σ)	1,406 (4,827)	746.87 (2,986.03)		968.41 (3,236.10)	
	Median (Q1-Q3)	176.08 (11.98-689.00)	17.97 (0.00-288.02)	*P*<0.0001	42.48 (0.00-468.70)	*P*<0.0001
	Min-max	0.00-65,527	0.00-50,060		0.00-36,145	
Medications	Mean (σ)	3,076 (9,131.20)	199,49 (409,72)		721.35 (747.43)	
	Median (Q1-Q3)	1,525 (1,037-2,185)	58.38 (11,84-220,45)	*P*<0.0001	523.35 (246.07-957.22)	*P*<0.0001
	Min-max	0.00-95,453	0.00-5,855		0.00-9,472	
Total costs	**Mean (σ)**	**14,020 (24,076)**	**3,564 (9,540)**		**6,418 (15,109)**	
	Median (Q1-Q3)	**4,624.70 (2,492-13,897)**	**824.75 (297.00-2,286)**	***P*<0.0001**	**1,904.82 (1,020-4,906)**	***P*<0.0001**
	Min-max	**105.03-253,160**	**0.00-190,380**		**0.00-193,294**	

Key: ED – emergency department.

The average cost of a patient with uncontrolled severe asthma who died was significantly higher than that of a surviving patient (€28,009 *vs*. €11,850.60; *P*<0.0001). Primary drivers of this increase in patients with uncontrolled severe asthma were hospitalizations (5-fold and 2-fold increases *vs*. the general and asthmatic populations, respectively), drugs of interest (16-fold and 4-fold increases *vs*. the general and asthmatic populations, respectively), and paramedical fees (2-fold and 1.4-fold increases *vs*. the general and asthmatic populations, respectively).

DISCUSSION

Given the lack of recent data quantifying impact of uncontrolled severe asthma on public health, the RESONANCE study provided important data characterizing this population and comparing it to the general and asthmatic populations in terms of morbidity and mortality as well as healthcare use and associated costs. This is the first study to specifically compare patients with uncontrolled severe asthma with the overall asthmatic population, in the French population.

The clinical burden of uncontrolled severe asthma was demonstrated through the increased risk of mortality, use of additional treatments (asthma-related treatment and other associated treatments), and hospitalizations during the 2-year follow-up period in comparison with matched patients from the general and asthmatic populations. The average costs of uncontrolled severe asthma to the healthcare system during the 2 years of follow-up represented nearly 4 times that of matched patients from the general population over the same period (difference of €10,456 per patient). This amounts to an increase of 293% in costs—more than twice that of matched asthmatic controls—in whom an increase of 118% in costs was seen over 2 years (difference of €7,601 per patient with the general population). *Bourdin et al*. found an incremental cost of $5,276 to the healthcare system annually when comparing patients with severe asthma to the general population, although a 2-year extrapolation would be biased due to the non-annual rate of care seeking in the study population.[12] However, no specific assessment of uncontrolled severe asthma was performed.

Hospitalizations were the main driver of healthcare use and costs, in line with other studies assessing the economic burden of asthma.[4,7,14] Costs during follow-up could have been influenced by the cost of hospitalization occurring at index date, since it was part of the selection criteria, given its connection with asthma non-control; however, the influence of this phenomenon was limited, as only 5.1% of patients were selected based solely on this criterion.

This study highlighted the excess healthcare costs during the last months of life in uncontrolled severe asthma, accounting for part of the excess cost associated with this condition overall, given their excess mortality rate during the follow-up period.

Our study also assessed the size of the uncontrolled severe patient population. The 739 patients identified among the total population of 16,588 patients with asthma suggest that this small but high-risk population represents 4.5% of all patients with asthma in France in 2014. When extrapolating to the entire adolescent and adult French population, this represents a prevalence of 0.15% (*i.e.*, 86,342 patients; 95% CI: 80,341, 92,789), which is slightly lower than other severe asthma populational estimates that used different definitions of asthma severity and did not account for asthma non-control.[12,15]

The uncontrolled severe asthmatic population was identified by means of a comprehensive algorithm, where great care was placed in the definitions of asthma, severity, and control to ensure the accuracy of the cohorts and palliate the lack of clinical data and use of a single marker, allowing identification of this unique population. Asthma was defined with robust data, such as asthma-related hospitalizations and complications, asthma-related full coverage for a long-term condition (ALD), and specific treatments.

Two cohorts were compared to patients with uncontrolled severe asthma. The objective of the general population control cohort was to highlight the absolute burden of uncontrolled severe asthma in the population. Matching on key sociodemographic characteristics aimed to control for potential confounding bias and ensure comparability of the populations, which was confirmed by standardized differences. In addition, a Cox regression model was developed post-hoc to compare mortality risk between the uncontrolled severe asthmatic cohort and the general population: impact of uncontrolled severe asthma on mortality was higher in patients without history of psychiatric disease compared to patients with history of psychiatric disease.

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The asthmatic control cohort was selected and matched to patients with uncontrolled severe asthma using propensity scores to control potential confounding factors using all available and relevant variables. A conservative approach was used, since some potential confounders included in propensity scores may be preponderant in patients with uncontrolled severe asthma, leading to a potential minimization of the burden of asthma lack of control and severity. More, given that this control population includes severe but controlled or non-controlled but non-severe patients with asthma, it is not a population exclusively comprising low-risk patients.

The study was conducted using the EGB, a well-recognized and robust populational medical administrative database that confers many advantages, such as the completeness of mortality data and comprehensiveness of healthcare reimbursed for all patients. Of note, the EGB does not include clinical information such as visit reason, diagnoses made outside hospitals, biological test results, or patients' anthropometric data.

The challenges associated with the use of administrative databases have been well documented. [16] In this study, the difficulties in selecting the patients with uncontrolled severe asthma were associated with potential measurement bias related to coding errors in hospital diagnoses; this source of error is likely limited and non-differential between groups. The algorithms assumed that filled prescriptions were proxies to treatment use; however, it is not possible to confirm that a filled prescription has been taken.

Potential indications of asthma treatments for other chronic pulmonary diseases such as COPD were accounted for, since an exclusion criterion based on ALD declarations or hospitalizations related to other chronic pulmonary diseases was considered. Despite this, some COPD patients may still have been included given the relatively old age of the asthmatic cohorts. It would occurred if ALD for COPD has not been declared, or if a patient has never been hospitalized during the last 5 years. Criterion requiring continuous insurance coverage may have resulted in a lower number of younger patients being included due to student-

specific insurance offered during school years; however, the impact of this limitation on the results is likely minimal.

Patients have been assigned to their group of interest (uncontrolled severe asthma, other patients with asthma, general population) at index date. Some patients may have evolved from non-asthma to asthma, or from asthma to uncontrolled severe asthma during follow-up and this was not considered in statistical analyses. However, given the duration of follow-up of two years, impact of such misclassification of patients during follow-up is probably limited.

The EGB offers the advantage of a limited number of patients lost to follow-up given the universal healthcare system present in France. It also has a few limitations: while most patients were covered by the general scheme, patients covered by other plans may not have been selected due to the later integration of those plans in the EGB. Also, the algorithm used to define asthma and index date excluded patients who died at the hospital around the time of the index date, thereby potentially excluding the most severe and uncontrolled patients. Finally, additional residual confounding factors may persist despite the matching process.

This large study allowing the comparison between patients with uncontrolled severe asthma and other patients with asthma and the general population, highlighted that severe asthma associated with non-control significantly affects mortality, healthcare use, and associated costs. This emphasized that close attention should be paid to ensure appropriate management of patients with severe asthma and monitoring of the level of control of asthma symptoms.

CONCLUSIONS

This database study demonstrates the huge burden of uncontrolled severe asthma in terms of mortality, morbidity, and healthcare resource consumption compared to other patients with asthma and the general population. These findings emphasize the importance of appropriate management in this high-risk population.

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Contributors All authors participated in the interpretation of the data, provided critical feedback and final approval for submission, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses. Stève Bénard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: all authors
Acquisition, analysis, or interpretation of data: all authors
Drafting of the manuscript: de Larrard and Bénard
Critical revision of the manuscript for important intellectual content: Roche, Demoly, Garcia, Cancalon, Perez, Mahieu and Vieu
Statistical analysis: de Larrard, Bénard and Cancalon
Administrative, technical, or material support: Bénard, Perez, Mahieu and Vieu
Supervision: all authors

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Competing interests Pr Pascal Demoly has received honoraria and/or research grants from ALK, Mylan-Viatris, Stallergènes, ThermoFisher Scientific, AstraZeneca, GSK, Novartis, Ménarini, and Regeneron.
Pr Gilles Garcia has received honoraria from ALK, Novartis, AstraZeneca, GSK, Sanofi and Chiesi for conferences or advisory board meetings.
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No other disclosures were reported.
Laurine Vieu, Aymeric Mahieu, Vincent Perez are Sanofi employee and may hold shares and/or stock options in the company.

Patient consent for publication Not required.

Data Availability Statement No additional data available.

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LIST OF FIGURE TITLES AND LEGENDS

FIGURE 1. RESONANCE study design

FIGURE 2. 24-month survival for the uncontrolled severe asthmatic cohort *vs.* general population and asthmatic control cohorts

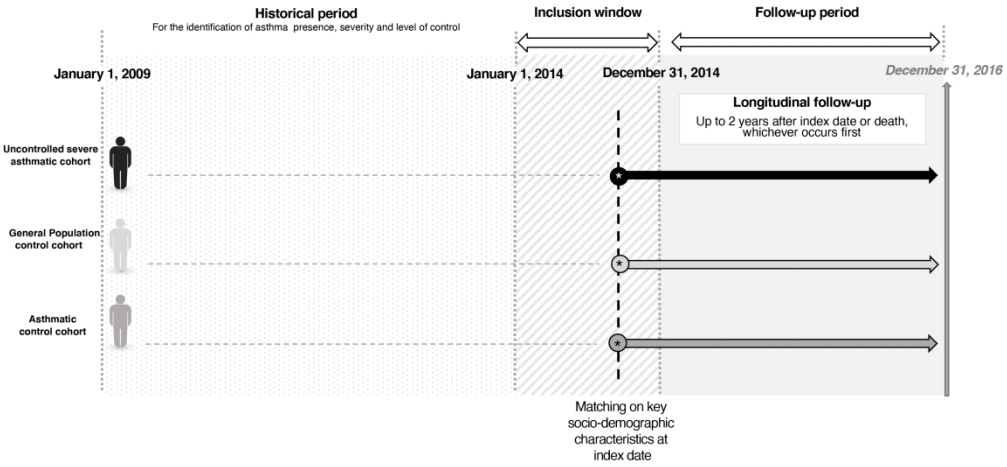

FIGURE 1. RESONANCE study design

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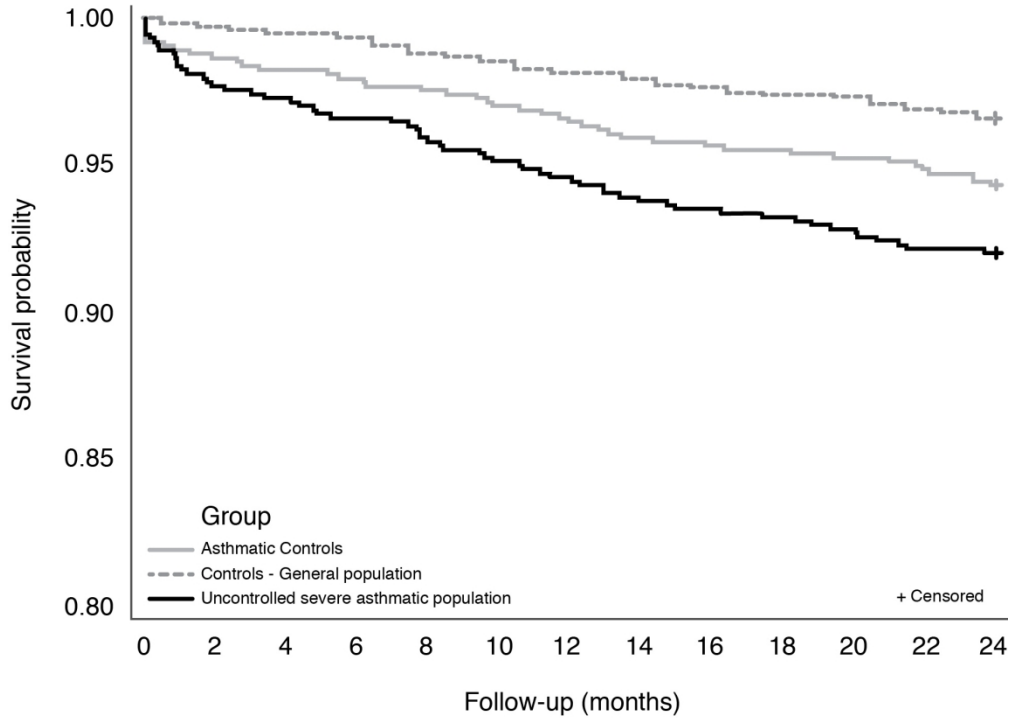


FIGURE 2. 24-month survival for the uncontrolled severe asthmatic cohort vs. general population and asthmatic control cohorts

166x119mm (300 x 300 DPI)

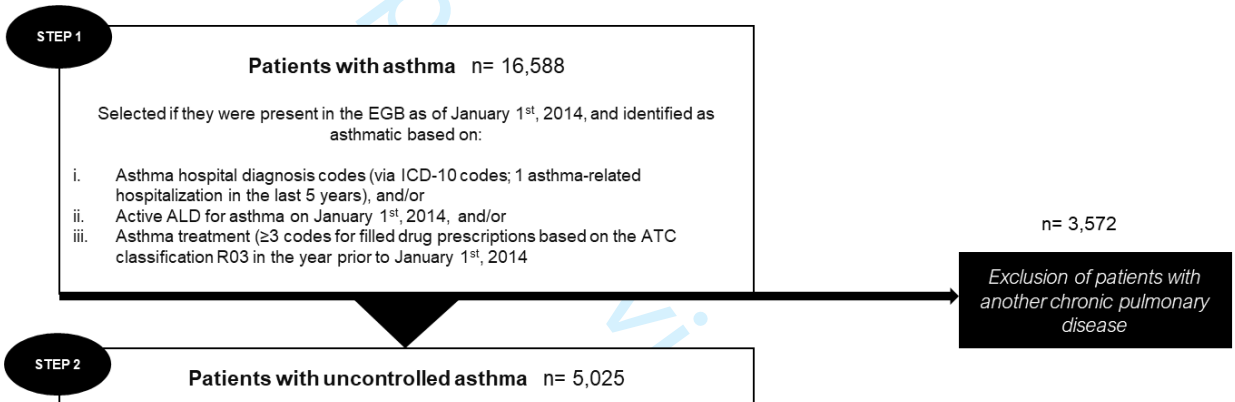
Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: findings from the retrospective observational RESONANCE study in France

Nicolas Roche[1], Gilles Garcia[2], Alexandre de Larrard[3], Charlotte Cancalon[3], Stève Bénard[3], Vincent Perez[4], Aymeric Mahieu[4], Laurine Vieu[4], Pascal Demoly[5]

Supplementary materials

FIGURE S1. Patient selection algorithm

Key: ALD – affection de longue durée (long-term condition); ATC – Anatomical Therapeutic Chemical; COPD – chronic obstructive pulmonary disease; ICD-10 – International Classification of Diseases, 10th Revision; ICS – inhaled corticosteroid; LABA – long-acting ß2-agonist; LAMA – long-acting muscarinic antagonist; OCS – oral corticosteroid; SABA – short-acting ß2-agonist.



Footnote:
** Of note, these criteria did not apply to patients with an ALD other than asthma (i.e. rheumatoid arthritis, ulcerative colitis, Crohn's disease, cancer, etc) who can be treated by OCS identified by an exploratory analysis of ALD of patients from the target population meeting criterion.*

Methods – Additional details on drugs of interest

Asthma treatments:

- short-acting beta2-agonists (SABA),
- long-acting beta2-agonists (LABA),
- long-acting anticholinergics (LAMA),
- antileukotriene receptor antagonists (LTRA),
- xanthines,
- inhaled and oral corticosteroids (ICS and OCS),
- combination treatments.

Other drug classes of interest:

- nasal antihistamines,
- antihistamines,
- nonsteroidal anti-inflammatory drugs (NSAIDs),
- antibiotics,
- proton pump inhibitors (PPIs),
- psychotropic drugs,
- topical corticosteroids,
- topical immunosuppressants.

Methods – ICD-10 codes used

For Asthma definition

J45.0 Predominantly allergic asthma
J45.1 Non-allergic asthma
J45.8 Mixed asthma
J45.9 Asthma, Unspecified
J46 Status asthmaticus
J96 Respiratory failure, not elsewhere classified

For Other chronic pulmonary disease definition

J41 Simple and mucopurulent chronic bronchitis
J42 Unspecified chronic bronchitis
J43 Emphysema
J44 Other chronic obstructive pulmonary disease
J47 Bronchiectasis
J61 Pneumoconiosis due to asbestos and other mineral fiber
J62.8 Pneumoconiosis due to other dust containing silica
J68.0 Bronchitis due to chemicals, gases, fumes and vapors
E84 Mucoviscidosis
J92.0 Pleural plaque with presence of asbestos
J94.8 Other specified pleural conditions
J96.1+0 Insuffisance respiratoire chronique obstructive

Methods – Variables defined for propensity score matching

1. nasal corticosteroid (Yes/No)
2. systemic antihistamine (Yes/No)
3. non-steroidal anti-inflammatory drugs (Yes/No)
4. antibiotic (Yes/No)
5. proton pump inhibitor (Yes/No)
6. dermocorticoids (Yes/No)
7. psychotropic drug (Yes/No)
8. age (years)
9. number of outpatient consultations
10. charlson's score
11. consultation with a nurse (Yes/No)
12. cardio-vascular diseases (Yes/No)
13. ocular antihistamine (Yes/No)
14. hypertension (Yes/No)
15. osteoporosis (Yes/No)
16. number of consultations with a physiotherapist
17. consultations with a physiotherapist (Yes/No)
18. depression (Yes/No)
19. psychiatric illness (Yes/No)
20. number of emergency room visits
21. hospitalization (Yes/No)
22. number of consultations with a nurse
23. emergency room visits (Yes/No)
24. number of hospitalizations
25. nasal antihistamine (Yes/No)
26. cataract (Yes/No)
27. nasal polyposis (Yes/No)
28. number of hospital consultations
29. gastroesophageal reflux (Yes/No)
30. dyslipidemia (Yes/No)
31. arrhythmia (Yes/No)
32. hospital consultations (Yes/No)
33. cerebrovascular diseases (Yes/No)
34. anxiety (Yes/No)
35. rhinosinusitis (Yes/No)
36. heart failure (Yes/No)
37. diabetes (Yes/No)
38. coronary heart disease (Yes/No)
39. sex
40. psychotic disorders (Yes/No)
41. outpatient consultation (Yes/No)
42. topical immunosuppressant (Yes/No)
43. CMU (Yes/No)
44. myocardial infarction (Yes/No)
45. atopic dermatitis (Yes/No)

TABLE S1. Quality of direct matching between cohort of patients with uncontrolled severe asthma and general population

Matching variables	*Before Matching*			*After Matching*		
	Uncontrolled severe asthma cohort (n=739)	**General population (n=466,977)**	**Standardized mean differences**	**Uncontrolled severe asthma cohort (n=739)**	**General population (n=2,217)**	**Standardized mean differences***
Age (mean, SD)	62.0 (16.7)	48.5 (20.2)	0.7297	62.0 (16.7)	62.0 (16.7)	0.0000
Sex						
Male (n, %)	318 (43.0%)	228 841 (49.0%)	0.1201	318 (43.0%)	954 (43.0%)	0.0000
Female (n, %)	421 (57.0%)	238 136 (51.0%)		421 (57.0%)	1 263 (57.0%)	
Beneficiary of CMU-c (n, %)	74 (10.0%)	31 778 (6.8%)	0.1158	74 (10.0%)	222 (10.0%)	0.0000

* A standardized mean difference < 0,1 after matching is considered as acceptable.

TABLE S2. Quality of propensity score matching between cohort of patients with uncontrolled severe asthma and cohort of patients with asthma

Matching variables	*Before Matching*			*After Matching*		
	Uncontrolled severe asthma cohort (n=739)	**Asthma cohort (n=15,849)**	**Standardized mean differences**	**Uncontrolled severe asthma cohort (n=739)**	**Asthma cohort (n=739)**	**Standardized mean differences***
Age (mean, SD)	62.0 (16.7)	54.8 (20.9)	0.3826	62.0 (16.7)	63.2 (17.2)	-0.0688
Sex						
Male (n, %)	318 (43.0%)	7 010 (44.2%)	0.0242	318 (43.0%)	347 (47.0%)	0.0789
Female (n, %)	421 (57.0%)	8 839 (55.8%)		421 (57.0%)	392 (53.0%)	
Beneficiary of CMU-c (n, %)	74 (10.0%)	1 536 (9.7%)	0.0108	74 (10.0%)	57 (7.7%)	0.0810
Cardiovascular diseases (n, %)	405 (54.8%)	6 863 (43.3%)	0.2316	405 (54.8%)	431 (58.3%)	-0.0710
Coronary heart disease (n, %)	55 (7.4%)	1 036 (6.5%)	0.0355	55 (7.4%)	69 (9.3%)	-0.0684
Myocardial infarction (n, %)	8 (1.1%)	179 (1.1%)	-0.0045	8 (1.1%)	8 (1.1%)	0.0000
Arrhythmia (n, %)	60 (8.1%)	946 (6.0%)	0.0841	60 (8.1%)	65 (8.8%)	-0.0243
Heart failure (n, %)	33 (4.5%)	527 (3.3%)	0.0590	33 (4.5%)	49 (6.6%)	-0.0947
Hypertension (n, %)	364 (49.3%)	6 178 (39.0%)	0.2081	364 (49.3%)	375 (50.7%)	-0.0298
Cerebrovascular diseases (n, %)	27 (3.7%)	411 (2.6%)	0.0610	27 (3.7%)	29 (3.9%)	-0.0142
Dyslipidemia (n, %)	237 (32.1%)	4 439 (28.0%)	0.0887	237 (32.1%)	268 (36.3%)	-0.0885

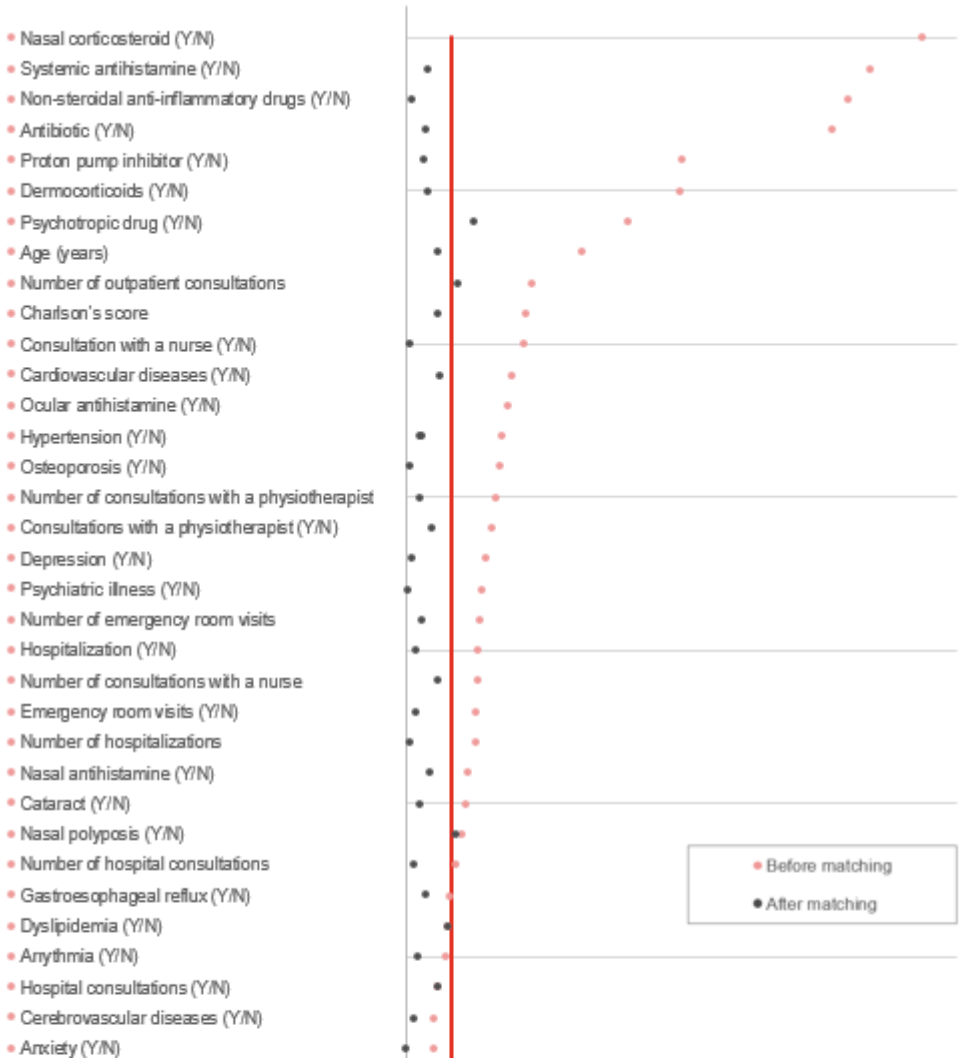
Diabetes (n, %)	108 (14.6%)	2 047 (12.9%)	0.0493	108 (14.6%)	112 (15.2%)	-0.0152
Osteoporosis (n, %)	110 (14.9%)	1 325 (8.4%)	0.2046	110 (14.9%)	112 (15.2%)	-0.0076
Psychiatric illness** (n, %)	224 (30.3%)	3 671 (23.2%)	0.1621	224 (30.3%)	223 (30.2%)	0.0029
Cataract (n, %)	75 (10.1%)	1 049 (6.6%)	0.1276	75 (10.1%)	69 (9.3%)	0.0274
Rhinosinusitis (n, %)	3 (0.4%)	17 (0.1%)	0.0591	3 (0.4%)	2 (0.3%)	0.0233
Gastroesophageal reflux (n, %)	79 (10.7%)	1 261 (8.0%)	0.0941	79 (10.7%)	69 (9.3%)	0.0451
Atopic dermatitis (n, %)	1 (0.1%)	22 (0.1%)	-0.0009	1 (0.1%)	0 (0.0%)	0.0521
Nasal polyposis (n, %)	14 (1.9%)	91 (0.6%)	0.1198	14 (1.9%)	5 (0.7%)	0.1083
Nasal antihistamine (n, %)	1 (0.1%)	197 (1.2%)	-0.1342	1 (0.1%)	3 (0.4%)	-0.0521
Ocular antihistamine (n, %)	4 (0.5%)	589 (3.7%)	-0.2213	4 (0.5%)	6 (0.8%)	-0.0330
Systemic antihistamine (n, %)	65 (8.8%)	7 892 (49.8%)	-1.0090	65 (8.8%)	75 (10.1%)	-0.0462
Nasal corticosteroid (n, %)	10 (1.4%)	6 597 (41.6%)	-1.1249	10 (1.4%)	15 (2.0%)	-0.0525
Non-steroidal anti-inflammatory drugs (n, %)	70 (9.5%)	7 756 (48.9%)	-0.9634	70 (9.5%)	73 (9.9%)	-0.0137
Antibiotic (n, %)	170 (23.0%)	10 249 (64.7%)	-0.9251	170 (23.0%)	184 (24.9%)	-0.0444
Proton pump inhibitor (n, %)	122 (16.5%)	6 776 (42.8%)	-0.6001	122 (16.5%)	132 (17.9%)	-0.0359
Psychotropic drug (n, %)	128 (17.3%)	6 091 (38.4%)	-0.4844	128 (17.3%)	172 (23.3%)	-0.1484
Dermocorticoids (n, %)	19 (2.6%)	3 321 (21.0%)	-0.5954	19 (2.6%)	25 (3.4%)	-0.0478
Topical immunosuppressant (n, %)	1 (0.1%)	31 (0.2%)	-0.0148	1 (0.1%)	0 (0.0%)	0.0521
Outpatient consultation (n, %)	656 (88.8%)	14 159 (89.3%)	-0.0182	656 (88.8%)	668 (90.4%)	-0.0532
Hospital consultation (n, %)	193 (26.1%)	3 685 (23.3%)	0.0665	193 (26.1%)	171 (23.1%)	0.0691
Consultation with a nurse (n, %)	551 (74.6%)	9 941 (62.7%)	0.2572	551 (74.6%)	548 (74.2%)	0.0093
Consultation with a physiotherapist (n, %)	383 (51.8%)	6 754 (42.6%)	0.1853	383 (51.8%)	363 (49.1%)	0.0541
Hospitalization (n, %)	468 (63.3%)	8 834 (55.7%)	0.1551	468 (63.3%)	475 (64.3%)	-0.0197
Emergency room visits (n, %)	356 (48.2%)	6 442 (40.6%)	0.1519	356 (48.2%)	349 (47.2%)	0.0190
Number of outpatient consultations (mean, SD)	36.9 (30.0)	29.2 (25.9)	0.2724	36.9 (30.0)	33.7 (26.7)	0.1128
Number of hospital consultations (mean, SD)	3.4 (10.2)	2.4 (7.9)	0.1094	3.4 (10.2)	3.3 (10.0)	0.0175
Number of consultations with a nurse (mean, SD)	53.5 (195.3)	27.9 (132.7)	0.1535	53.5 (195.3)	41.6 (162.1)	0.0665
Number of consultations with a physiotherapist (mean, SD)	37.0 (98.8)	21.1 (62.3)	0.1935	37.0 (98.8)	34.1 (104.0)	0.0286
Number of hospitalizations (mean, SD)	2,.3 (5.0)	1.6 (4.0)	0.1514	2.3 (5.0)	2.4 (5.0)	-0.0057

Number of emergency room visits (mean, SD)	1.2 (2.2)	0.9 (1.9)	0.1606	1.2 (2.2)	1.2 (1.9)	0.0340
Charlson's score (mean, SD)	3.6 (2.3)	3.0 (2.3)	0.2588	3.6 (2.3)	3.8 (2.4)	-0.0702

* A standardized mean difference < 0,1 after matching is considered as acceptable.

**Psychiatric illness includes depression, anxiety, and psychotic disorders.

FIGURE S2. Quality of propensity score matching between cohort of patients with uncontrolled severe asthma and cohort of patients with asthma



A standardized mean difference < 0,1 after matching is considered as acceptable.

FIGURE S3. Analysis of mortality by age group

Age group	Target population	Deceased target population	Asthmatic control cohort	Deceased asthmatic control cohort	RR	95% CI	RRR
[50;60[	140	6	135	1	5,79	[0,71;47,41]	-4,79
[60;70[	183	15	151	3	4,13	[1,22;13,97]	-3,13
[70;80[	136	14	161	10	1,66	[0,76;3,60]	-0,66
[80;90[	86	15	117	16	1,28	[0,68;2,41]	-0,28
≥90	28	9	21	12	0,56	[0,40;0,79]	0,44

Target population: Uncontrolled severe asthmatic cohort

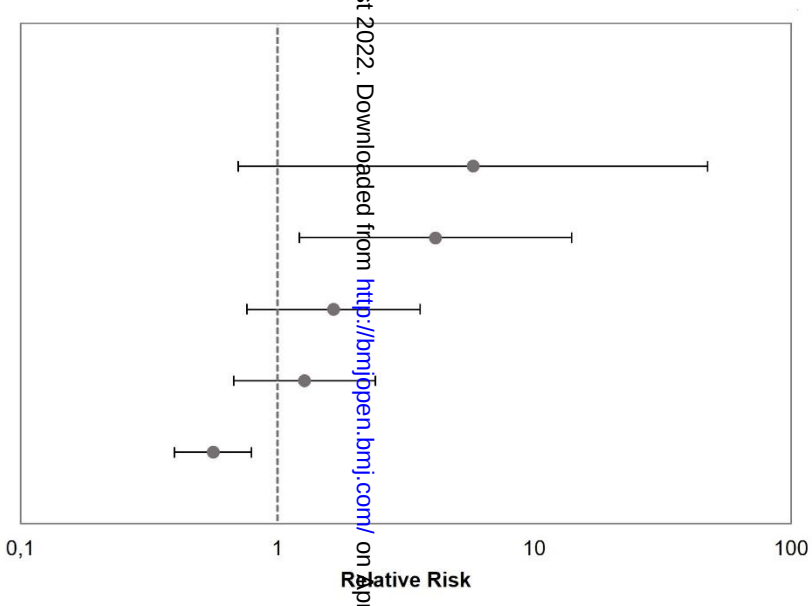
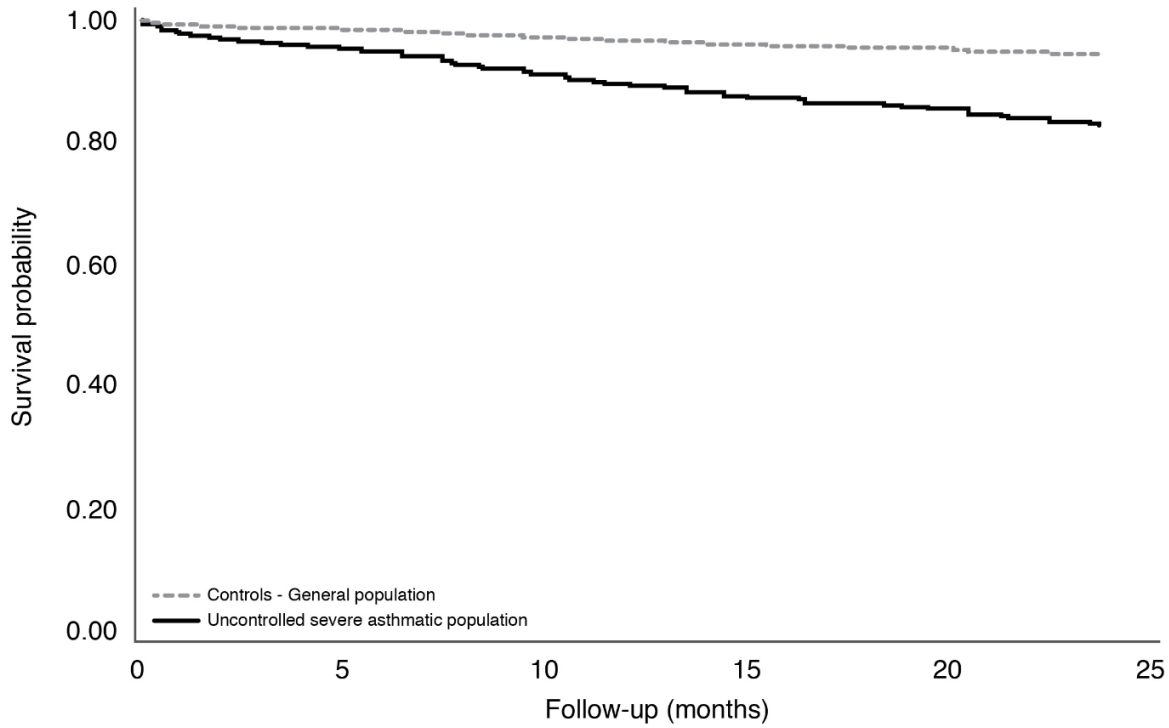


Table S3. Results of multivariate Cox model on mortality

Covariate	Hazard ratio	95% CI
Age (1-year increase)	1.07	1.05 - 1.09
History of cardiovascular diseases (with *vs.* without)	1.91	1.18 - 3.09
History of diabetes (with *vs.* without)	1.66	1.11 - 2.49
History of cancer (with *vs.* without)	2.40	1.64 - 3.50
Patients with uncontrolled severe asthma *vs.* general population in population with history of psychiatric disease	1.22	0.66 - 2.26
Patients with uncontrolled severe asthma *vs.* general population in population without history of psychiatric disease	3.25	2.14 - 4.92

Key: CI – confidence interval.

FIGURE S4. 24-month survival for the uncontrolled severe asthmatic cohort versus general population among subjects without history of psychiatric disease



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7 (Figure S1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-16

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-16
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: findings from the retrospective, observational RESONANCE study in France

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Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: findings from the retrospective, observational RESONANCE study in France

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ABSTRACT

Objective: To characterize uncontrolled severe asthma and compare the disease burden with the general and asthmatic populations.

Design: Retrospective observational study using a national sample of a French healthcare database (*Echantillon Généraliste des Bénéficiaires [EGB])*.

Setting: The EGB, an anonymized permanent sample of health insurance databases, representing 1/97th of the French population.

Participants: Patients (≥12 years) were selected in year 2014 and followed 2 years. A cohort of patients with uncontrolled severe asthma was defined using an algorithm based on peer-reviewed literature and Global Initiative for Asthma recommendations. Index date was the occurrence of the first marker of uncontrolled asthma. This cohort was matched with 2 control cohorts, general population and asthmatic controls, on baseline characteristics.

Main outcomes measures: Mortality, healthcare use, and associated costs were studied in the 2 years of follow-up.

Results: Among 467,716 individuals in the EGB, 16,588 patients with asthma were identified, including 739 (4.5%) with uncontrolled severe disease. The survival probability at 2 years for patients with uncontrolled severe asthma (92.0%) was lower than in the general population cohort (96.6%; relative risk of death: 2.35; 95% confidence interval: 1.70-3.29; *P*<0.0001) and tended to be lower than in the control asthmatic cohort (94.3%; *P*=0.07). Emergency department visits and hospitalizations were higher in patients with uncontrolled severe asthma than in the general population (64.7% *vs.* 34.9%; *P*<0.0001) and asthmatic controls (64.7% *vs.* 55.2%; *P*=0.0002). Other components of healthcare use (medical and paramedical visits, medications) were increased in patients with uncontrolled severe asthma compared with control populations. These increases translated into higher costs (*P*<0.0001 for both comparisons).

Conclusions: This study demonstrates the huge burden of uncontrolled severe asthma in terms of mortality, morbidity, and healthcare resource consumption compared with other patients with asthma and with the general population and emphasizes the importance of appropriate management in this high-risk population.

Strengths and limitations of this study

- The study was conducted using a well-recognized and robust populational medical administrative database that confers many advantages, such as the completeness of mortality data and comprehensiveness of healthcare reimbursed for all patients.
- This is the first study, to our knowledge, to specifically compare patients with uncontrolled severe asthma with the overall asthmatic population, in the French population.
- Comparability of studied groups was ensured by careful matching process.
- The lack of clinical data was mitigated by the use of a comprehensive algorithm to identify the uncontrolled severe asthmatic population with great care in the definitions of asthma, severity, and control to ensure the accuracy of the cohorts.
- The criteria requiring continuous insurance coverage may have resulted in a marginally lower number of younger patients being included due to student-specific insurance offered during school years.

INTRODUCTION

Asthma is one of the most common chronic diseases and is a major cause of morbidity. This heterogeneous disease is characterized by its chronic inflammatory nature which can lead to airway remodeling and presents with varied levels of severity and control. While a majority of patients with asthma have mild to moderate disease according to Global Initiative for Asthma (GINA) criteria, between 3% and 10% present a severe asthma, which may be life-threatening, particularly due to severe and potentially fatal exacerbations.[1,2] Despite implementation of an optimal management strategy, many patients with severe asthma are not able to achieve disease control, leading to poor quality of life and significant social and health burdens. Therefore, asthma represents an important public health issue given its impact on work productivity (*i.e.*, absenteeism and presenteeism) and the costs associated with disease management and healthcare resource utilization.[3–7]

In the context of the rapidly evolving landscape of expensive GINA step 5 asthma treatments, it is crucial to generate up-to-date data on the real-life population burden of uncontrolled severe asthma in adolescents and adults and to understand the relative impact of the disease in patients with severe asthma compared to the general and to non-severe asthmatic populations. The framework of the French Health Data Hub project provided the opportunity to access the public medico-administrative database to address this specific issue.

The RESONANCE study was undertaken to: (1) characterize uncontrolled severe asthma in patients aged 12 years and older, and (2) compare the disease burden in terms of mortality, healthcare utilization, and associated costs within this population to two series of matched controls from the general population and the asthmatic population (*i.e.* total asthmatic population excluding those with uncontrolled severe asthma).

METHODS

Study Design

A retrospective, non-interventional cohort study was carried out using a large populational database from France, the *Echantillon Généraliste des Bénéficiaires* (EGB). All individuals aged 12 years and over in the EGB were included in the source population. A cohort of adolescent and adult patients who had uncontrolled severe asthma during 2014 were identified. Their index date was the date of the first event identifying non-control during 2014. Two control cohorts were defined, one from the general population and another of patients with asthma. For each selected control, the assigned index date was the calendar index date of respective matched patients from the uncontrolled severe asthma cohort.

Historical information on comorbidities, healthcare use, and treatments received were collected up to five years preceding the index date to assess baseline characteristics. Socio-demographic characteristics were collected at index date for the three cohorts. Cohorts were followed up to two years after the index date or death, whichever occurs first, to assess the outcomes of interest (Figure 1).

Data sources

The EGB is an anonymized permanent sample of health insurance databases representing 1/97th of the entire French population.[8,9] Given the universal healthcare system in France, the EGB is a sizeable and representative sample of all subjects covered by various social security schemes, and now includes nearly 660,000 beneficiaries.

The EGB contains information on demographics (age, sex, area of residence, etc.); outpatient care reimbursement (including drug dispensing); medical care and reimbursement received in outpatient and hospital settings; specific information on the right to universal supplementary health coverage (CMU-c); whether beneficiaries are affected by a long-term condition (*affection de longue durée*; ALD); and the date of death. The database benefits from the

interlinkage of several administrative data sources, thereby allowing an assessment of beneficiaries' healthcare utilization over time.

Subjects

Patients with uncontrolled severe asthma were identified using an algorithm based on events occurring in 2014 (Figure S1, Supplementary File). This algorithm was designed following a literature review,[10–12] and GINA management recommendations,[13] in collaboration with an expert scientific committee composed of 3 respiratory specialists.

Patients with evidence of another chronic pulmonary disease, including chronic obstructive pulmonary disease (COPD), identified through International Classification of Diseases, 10th Revision (ICD-10) codes related to hospital diagnoses or ALD, were excluded (Supplementary File).

Controls from general population were randomly selected among all individuals, besides patients with uncontrolled severe asthma, present in the EGB in 2014. Controls were matched with patients in the uncontrolled severe asthma cohort on age, sex, and CMU-c status at index date. Up to 3 controls per case were selected. Direct matching quality was assessed by comparing standardized differences between both cohorts (Table S1, Supplementary File).

Individuals in the asthma cohort were randomly selected within the total asthmatic population present in the EGB in 2014, excluding those with uncontrolled severe asthma. Individuals were matched with patients in the uncontrolled severe asthma cohort on a 1:1 ratio, using nearest neighbour propensity score matching. Propensity scores incorporated 45 variables recommended by the expert scientific committee, including sociodemographic characteristics, comorbidities, and history of healthcare use prior to index date. Standardized differences were used to assess matching quality (Table S2, Supplementary File).

Collected data and outcomes

The following sociodemographic and clinical characteristics were considered:

- Up to 5 years prior to index date: comorbidities, treatments received, healthcare utilization (medical visits, emergency department [ED] visits, hospitalizations)
- At index date: age, sex, CMU-c status
- During follow-up:
    - Date of death, if applicable
    - Drugs of interest: asthma treatments and other classes of interest (Supplementary File)
    - Healthcare utilization: Medical and paramedical visits (general medicine, respiratory specialists, otolaryngology, nursing support, physiotherapy), ED visits, and hospitalizations (all-cause and asthma-related)
    - Direct medical costs associated with medications and healthcare use (outpatient and hospital settings)

The primary objective of this study was to assess the number and proportion of patients with uncontrolled severe asthma aged 12 and older. Sociodemographic and clinical characteristics were provided for this population.

The secondary objective was to assess all-cause mortality and survival probability, healthcare use and associated costs in the 2 years after index date in the uncontrolled severe asthma cohort compared to the two matched control cohorts (general population and asthmatic controls).

Statistical analyses

Continuous variables were described using means, standard deviations, medians, and ranges, whilst categorical variables were described as frequencies.

Crude cumulative all-cause mortality rates at 2 years were obtained for all cohorts using the Kaplan-Meier methodology, whereby the probability of survival from index date through follow-up was estimated. The comparative analyses of mortality, healthcare utilization, and

associated costs between the primary cohort and matched controls were conducted using paired Student's *t*-tests or Wilcoxon signed-rank tests for quantitative variables according to their distribution, and Mc Nemar tests for qualitative variables. A post-hoc analysis using a Cox regression model was built to compare mortality between the uncontrolled severe asthmatic cohort and general population. The final model included the following variables: population (uncontrolled severe asthmatic cohort *vs*. general population), age, history of cardiovascular disease, diabetes, psychiatric disease, and cancer. Interaction terms between the variable "population" and other covariates included in the model were tested. Interaction between population and history of psychiatric disease was significant and was thus included in the final model, with other variables listed above. Costs were evaluated from the collective perspective, and all costs collected between 2014 and 2016 were reevaluated to correspond to 2018 Euros (€) using the 2018 consumer price index (health data index 4011-E, published by national institute of statistics and economic studies, *Institut National de la Statistique et des Études Économiques*, *INSEE*), since 2018 was the date of data access. All analyses were performed using the SAS 9.4 software package (SAS Institute, Cary, NC, USA).

Ethical considerations

Used data were anonymized to ensure confidentiality at the patient level. Data handling, processing, and analysis were carried out in alignment and with authorizations from an independent committee (*CEREES, Comité d'Expertise pour les Recherches, les Études et les Évaluations dans le domaine de la Santé*; favorable opinion on June 14, 2018; TPS 31996) and from the French National Data Protection Agency *(CNIL, Commission Nationale de l'Informatique et des Libertés*; Authorization DR-2018-097).

Patient and Public Involvement Statement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Population selection

Of the 467,716 adolescents and adults present in the EGB, a total of 16,588 patients with asthma were identified and 5,025 of these exhibited a marker of uncontrolled disease in 2014 (Figure S1, Supplementary File). Among these, 739 patients with uncontrolled severe asthma were identified (57% female; mean age: 62.0 years; 10.0% with CMU-c, Tables S1 and S2, Supplementary File).

A total of 2,217 matched individuals were selected to build the control cohort from the general population (Table S1, Supplementary File). The control asthmatic population (all patients with asthma excluding those with uncontrolled severe asthma) included 739 patients matched to patients with uncontrolled severe asthma using propensity scores (53.0% women; mean age: 63.2 years; 7.7% with CMU-c, Table S2, Supplementary File). The majority of the 45 variables defined for matching were successfully balanced (Table S2 and Figure S2, Supplementary File).

Mortality

In total, 59 patients with uncontrolled severe asthma died during the 2-year follow-up period. The probability of survival at 2 years in this cohort was 92.0%, which was lower than that observed in the matched control cohort from the general population (96.6%; relative risk [RR] of death: 2.35; 95% CI: 1.70, 3.29; *P*<0.0001). An increased mortality risk was notably seen among those aged 50 to <60 years old (RR: 18.0; 95% CI: 2.2, 148.2), and those aged 60 to <70 years old (RR: 4.1; 95% CI: 1.9, 8.7). While the asthmatic control cohort had a numerically higher survival probability at 2 years than the uncontrolled severe asthmatic cohort, the difference was not significant (94.3% *vs.* 92.0%; *P*=0.0747). However, the analysis of mortality by age group showed a higher risk of mortality in patients aged 60 to <70 years (8% *vs*. 2% deaths in uncontrolled severe asthmatic cohort *vs.* asthmatic control cohort; RR: 4.1; 95% CI: 1.2, 14.0; Figure S3, Supplementary File).

Compared with both control cohorts, the increased risk of mortality in uncontrolled severe asthma cohort was observed early, and became higher during follow-up (Figure 2).

Due to a significant interaction between population (uncontrolled severe asthma or general population) and history of psychiatric disease in the Cox model assessing mortality risk, impact of population was assessed by history of psychiatric disease, and impact of history of psychiatric disease was assessed by population (Table S3, Supplementary File). Uncontrolled severe asthma increased mortality risk, only for patients without history of psychiatric disease (hazard ratio [HR]: 3.25; 95% CI: 2.14, 4.92). The difference in mortality risk between patients with uncontrolled severe asthma and general population was not significant in patients with history of psychiatric disease (HR: 1.22; 95% CI: 0.66, 2.26). Comorbidities (age, history of cardiovascular disease, diabetes, and cancer) increased mortality risk, especially cancer (HR: 2.40; 95% CI: 1.64, 3.50). Among subjects without history of psychiatric disease, overall survival was lower in the uncontrolled severe asthmatic cohort compared to general population, with a difference of 10% at 24 months (Figure S4, Supplementary File).

Healthcare utilization

Table 1 shows the level of healthcare utilization for all three cohorts during follow-up. The proportion of patients requiring medical care in the hospital setting at least once during follow-up was higher in the uncontrolled severe asthmatic population compared to both control populations.

Table 1. Comparison of the results for mortality and main healthcare use per patient during the 2-year follow-up

	Cohort of uncontrolled severe asthmatics (N=739)	General population cohort (N=2,217)	*P*-Value	Asthmatic control cohort (n=739)	*P*-Value
Deaths, n (%)	**59 (8.0)**	**75 (3.4)**	***P*<0.0001**	**42 (5.7)**	***P*=0.0747**
Deaths by age group, n (%)					
<20	0 (0.0)	0 (0.0)		0 (0.0)	
20-<30	0 (0.0)	1 (1.3)		0 (0.0)	
30-<40	0 (0.0)	1 (1.3)		0 (0.0)	
40-<50	0 (0.0)	1 (1.3)	*P*=0.0393	0 (0.0)	*P*=0.0366
50-<60	6 (10.2)	1 (1.3)		1 (2.4)	
60-<70	15 (25.4)	11 (14.7)		3 (7.1)	
70-<80	14 (23.7)	16 (21.3)		10 (23.8)	
80-<90	15 (25.4)	20 (26.7)		16 (38.1)	
≥90	9 (15.3)	24 (32.0)		12 (28.6)	
Mean age at death (σ)	**76.1 (12.5)**	**79.7 (14.5)**	*P*=0.0266	83.0 (9.7)	*P*=0.0037
Min-max	51.0-102.0	25.0-100.0		55.0-102.0	
At least 1 medical care act done at hospital, n (%)	**478 (64.7)**	**774 (34.9)**	***P*<0.0001**	**408 (55.2)**	***P*=0.0002**
ED visit	318 (43.0)	465 (21.0)	*P*<0.0001	247 (33.4)	*P*=0.0002
All-cause hospitalization	409 (55.3)	556 (25.1)	*P*<0.0001	349 (47.2)	*P*=0.0023
Asthma-related hospitalizations (asthma and severe exacerbation)[a]	27 (3.7)	0 (0.0)	NA	12 (1.6)	*P*=0.0163
Asthma-related hospitalizations with at least 1 visit in intensive care unit	3 (0.4)	0 (0.0)	NA	1 (0.1)	0.3173
At least 1 medical visit during follow-up, n (%)	**708 (95.8)**	**1,995 (90.0)**	***P*<0.0001**	**709 (95.9)**	***P*=0.8981**
General practitioner	602 (81.5)	1,628 (73.4)	*P*<0.0001	620 (83.9)	*P*=0.2185
Respiratory specialist	94 (12.7)	53 (2.4)	*P*<0.0001	42 (5.7)	*P*<0.0001
Ear-nose-throat specialist	67 (9.1)	122 (5.5)	*P*<0.0001	37 (5.0)	*P*=0.0030
At least 1 paramedical visit during follow-up, n (%)	**600 (81.2)**	**1,390 (62.7)**	***P*<0.0001**	**546 (73.9)**	***P*=0.0011**
Nurse consultation	531 (71.9)	1,184 (53.4)	*P*<0.0001	496 (66.7)	*P*=0.0353
Physiotherapy consultation	320 (43.3)	673 (30.4)	*P*<0.0001	259 (35.0)	*P*=0.0013
At least 1 filled prescription for an asthma medication during follow-up, n (%)	**726 (98.2)**	**257 (11.6)**	***P*<0.0001**	**638 (86.3)**	***P*<0.0001**
Short-acting bronchodilator	606 (82.0)	100 (4.5)	*P*<0.0001	396 (53.6)	*P*<0.0001
Long-acting bronchodilator: LAMA/LABA	316 (42.8)	53 (2.4)	*P*=0.0004	190 (25.7)	*P*<0.0001
Long-acting bronchodilator: xanthines	56 (7.6)	2 (0.1)	*P*<0.0001	10 (1.4)	*P*<0.0001
Anti-inflammatory medication (ICS ± OCS)	506 (68.5)	115 (5.2)	*P*<0.0001	273 (36.9)	*P*<0.0001
Anti-inflammatory medication (ICS ± OCS) and long-acting bronchodilator	626 (84.7)	128 (5.8)	*P*<0.0001	413 (55.9)	*P*<0.0001

	Cohort of uncontrolled severe asthmatics (N=739)	General population cohort (N=2,217)	*P*-Value	Asthmatic control cohort (n=739)	*P*-Value
At least 1 visit to a GP, respiratory specialist, or allergy specialist, followed within 10 days by a filled prescription of OCS, n (%)	481 (65.1)	447 (20.2)	*P*<0.0001	229 (31.0)	*P*<0.0001
At least 1 filled prescription of a medication of interest during follow-up, n (%)	**727 (98.4)**	**1,847 (83.3)**	***P*<0.0001**	**678 (91.7)**	***P*<0.0001**
Intranasal antihistamines	22 (3.0)	13 (0.6)	*P*<0.0001	10 (1.4)	*P*=0.0339
Ocular antihistamines	43 (5.8)	80 (3.6)	*P*=0.0004	27 (3.7)	*P*=0.0523
Systemic antihistamines	488 (66.0)	675 (30.4)	*P*<0.0001	273 (36.9)	*P*<0.0001
Intranasal corticosteroids	420 (56.8)	567 (25.6)	*P*<0.0001	230 (31.1)	*P*<0.0001
Nonsteroidal anti-inflammatory drugs	407 (55.1)	1,083 (48.8)	*P*<0.0001	317 (42.9)	*P*<0.0001
Antibiotics	670 (90.7)	1,323 (59.7)	*P*<0.0001	501 (67.8)	*P*<0.0001
Proton-pump inhibitors	506 (68.5)	980 (44.2)	*P*<0.0001	348 (47.1)	*P*<0.0001
Psychotropic drugs	426 (57.6)	840 (37.9)	*P*<0.0001	320 (43.3)	*P*<0.0001
Topical corticosteroids	235 (31.8)	512 (23.1)	*P*<0.0001	145 (19.6)	*P*<0.0001
Topical immunosuppressants	2 (0.3%)	1 (0.0)	*P*=0.0588	0 (0.0%)	NA

[a] Excluding stays of less than 1 night (or Z codes).

Key: ED – emergency department; GP – general practitioner; ICS – inhaled corticosteroid; LABA – long-acting ß2-agonist; LAMA – long-acting muscarinic antagonist; NA – not applicable; OCS – oral corticosteroid.

A 2-fold increase in ED visits and all-cause or asthma-related hospitalizations was observed for patients with uncontrolled severe asthma compared with the general population (64.7% *vs.* 34.9%; *P*<0.0001). Patients with uncontrolled severe asthma also had an increased use of other main components of care, such as medical visits (95.8% *vs*. 90.0%; *P*<0.0001) and paramedical visits (81.2% *vs*. 62.7%; *P*<0.0001) compared with the general population. An increased healthcare use was also highlighted in comparison with the asthmatic cohort, since patients with uncontrolled severe asthma had more ED visits and hospitalizations (64.7% *vs*. 55.2%; *P*=0.0002), and paramedical visits (81.2% *vs*. 73.9%; *P*=0.0011), compared with asthmatic controls.

For drug prescriptions, the proportion of patients receiving medications was higher in patients with uncontrolled severe asthma compared with matched individuals from the general population cohort, both in terms of asthma-related treatments including oral corticosteroid therapy (98.2% *vs*. 11.6%; *P*<0.0001), and other treatments, such as antibiotics, nonsteroidal anti-inflammatory drugs, and psychotropic drugs (98.4% *vs*. 83.3%; *P*<0.0001). Patients with uncontrolled severe asthma also had higher medication use than the asthmatic controls both for asthma-related treatments (98.2% *vs*. 86.3%; *P*<0.0001), and other medications (98.4% *vs*. 91.7%; *P*<0.0001).

Costs

Increase of healthcare use was translated into higher costs. Healthcare use mean costs per patient during the 2-year follow-up were higher for patients with uncontrolled severe asthma (€14,020) compared to the general population (€3,564; *P*<0.0001) or asthmatic controls (€6,418; *P*<0.0001), regardless of the expenditure (Table 2).

Table 2. Comparison of costs (reimbursement amounts, in Euros) associated with hospital and outpatient use, per patient, over a 2-year period after the index date (patients with uncontrolled severe asthma *vs.* general population and asthmatic control cohorts)

	Costs per patient	Cohort of patients with uncontrolled severe asthma (N=739)	General population cohort (N=2,217)	*P*-Value	Asthmatic control cohort (n=739)	*P*-Value
Hospitalization	Mean (σ)	8,163 (20,669)	1,800 (7,991)		3,589 (13,702)	
	Median	426 (0 - 5,854)	0 (0 - 0)	*P*<0.0001	0 (0 - 1,284)	*P*<0.0001
	Min-max	0 - 246,483	0 - 176,423		0 - 190,457	
ED visit without hospitalization	Mean (σ)	12 (28)	6 (18)		9 (33)	
	Median (Q1-Q3)	0 (0 - 25)	0 (0 - 0)	*P*<0.0001	0 (0 - 0)	*P*<0.0001
	Min-max	0 - 319	0 - 273		0 - 671	
Medical visits	Mean (σ)	643 (1,068)	368 (437)		496 (658)	
	Median (Q1-Q3)	491 (278 - 786)	265 (113 - 499)	*P*<0.0001	376 (217 - 612)	*P*<0.0001
	Min-max	0 - 24,882	0 - 6,861		0 - 11,547	
Laboratory tests	Mean (σ)	241 (321)	154 (266)		203 (285)	
	Median (Q1-Q3)	145 (53 - 295)	85 (0 - 180)	*P*<0.0001	126 (54 - 237)	*P*=0.0131
	Min-max	0 - 3,137	0 - 5,727		0 - 4,461	
Paramedical visits	Mean (σ)	1,406 (4,827)	747 (2,986)		968 (3,236)	
	Median (Q1-Q3)	176 (12 - 689)	18 (0 - 288)	*P*<0.0001	42 (0 - 469)	*P*<0.0001
	Min-max	0 - 65,527	0 - 50,060		0 - 36,145	
Medications	Mean (σ)	3,076 (9,131)	199 (410)		721 (747)	
	Median (Q1-Q3)	1,525 (1,037 - 2,185)	58 (12 - 220)	*P*<0.0001	523 (246 - 957)	*P*<0.0001
	Min-max	0 - 95,453	0 - 5,855		0 - 9,472	
Total costs	**Mean (σ)**	**14,020 (24,076)**	**3,564 (9,540)**		**6,418 (15,109)**	
	Median (Q1-Q3)	**4,625 (2,492 - 13,897)**	**825 (297 - 2,286)**	***P*<0.0001**	**1,905 (1,020 - 4,906)**	***P*<0.0001**
	Min-max	**105 - 253,160**	**0 - 190,380**		**0 - 193,294**	

Key: ED – emergency department.

The average cost of a patient with uncontrolled severe asthma who died was significantly higher than that of a surviving patient (€28,009 *vs*. €11,851; *P*<0.0001). Primary drivers of this increase in patients with uncontrolled severe asthma were hospitalizations (5-fold and 2-fold increases *vs*. the general and asthmatic populations, respectively), drugs of interest (16-fold and 4-fold increases *vs*. the general and asthmatic populations, respectively), and paramedical fees (2-fold and 1.4-fold increases *vs*. the general and asthmatic populations, respectively).

DISCUSSION

Given the lack of recent data assessing the impact of uncontrolled severe asthma on public health, the RESONANCE study provided important data characterizing this population and comparing it to the general and asthmatic populations in terms of morbidity and mortality, as well as healthcare use and associated costs. To our knowledge, this is the first study to specifically compare patients with uncontrolled severe asthma with the overall asthmatic population, in the French population.

The clinical burden of uncontrolled severe asthma was demonstrated through the increased risk of mortality, use of additional treatments (asthma-related treatment and other associated treatments), and hospitalizations during the 2-year follow-up period in comparison with matched patients from the general and asthmatic populations. The average cost of uncontrolled severe asthma for healthcare system during the 2 years of follow-up represented nearly 4 times (mean cost difference of €10,456 per patient) and more than 2 times (mean cost difference of €7,602 per patient) that of matched patients from the general population and from asthmatic control cohort, respectively, over the same period. *Bourdin et al*. found an annually incremental cost of $5,276 for healthcare system when comparing patients with severe asthma with the general population, although a 2-year extrapolation would be biased due to the non-annual rate of care seeking in the study population.[12] However, no specific assessment of uncontrolled severe asthma was performed.

Hospitalizations were the main driver of healthcare use and costs, in agreement with other studies assessing the economic burden of asthma.[4,7,14] Costs during follow-up could have been influenced by the cost of hospitalization occurring at index date, since hospitalization related to asthma was part of the selection criteria to identify asthma non-control; however, nfluence of this phenomenon was limited since only 5.1% of patients were selected based solely on this criterion.

This study highlighted the excess of healthcare costs during the last months of life in uncontrolled severe asthma, accounting for part of the excess cost associated with this condition overall, given their higher mortality rate during the follow-up period.

Our study also assessed the size of the uncontrolled severe asthma population. The 739 patients identified among the total population of 16,588 patients with asthma suggest that this small but high-risk population represented 4.5% of all patients with asthma in France in 2014. When extrapolating to the entire adolescent and adult French population, this represents a prevalence of 0.15% (*i.e.*, 86,342 patients; 95% CI: 80,341, 92,789), which is slightly lower than other severe asthma populational estimates that used different definitions of asthma severity and did not account for asthma non-control.[12,15]

The uncontrolled severe asthmatic population was identified by means of a comprehensive algorithm, with great care in the definitions of asthma, severity, and control to ensure the accuracy of the cohorts and palliate the lack of clinical data. Asthma was defined with robust data, such as asthma-related hospitalizations and complications, asthma-related full coverage for a long-term condition, and specific treatments.

Two cohorts were compared with patients with uncontrolled severe asthma. The objective of the general population control cohort was to highlight the absolute burden of uncontrolled severe asthma in the population. Matching on key sociodemographic characteristics aimed to control for potential confounding bias and ensure comparability between populations, which was confirmed by acceptable standardized differences. In addition, a Cox regression model was developed in post-hoc analysis to compare mortality risk between the uncontrolled severe asthmatic cohort and the general population: uncontrolled severe asthma was associated with increased mortality, only for patients without history of psychiatric disease. This increased risk was not found in patients with history of psychiatric disease, however the statistical model was only adjusted for age, history of cardiovascular disease, diabetes, and cancer but not for other

potential confounders such as psychotropic drugs use since we did not aim at assessing factors associated with mortality in subjects with a history of psychiatric disease.

The asthmatic control cohort was selected and matched with patients with uncontrolled severe asthma using propensity scores to control potential confounders, using all available and relevant variables. A conservative approach was used, since some potential confounders included in propensity scores may be preponderant in patients with uncontrolled severe asthma, leading to a potential minimization of the burden of asthma lack of control and severity. More, given that this control population includes severe but controlled or non-controlled but non-severe patients with asthma, it is not a population exclusively comprising low-risk patients.

The study was conducted using the EGB, a well-recognized and robust populational medical administrative database that confers many advantages, such as the completeness of mortality data and comprehensiveness of healthcare reimbursed for all patients. Of note, the EGB does not include clinical information such as visit reason, diagnoses made outside hospitals, biological test results, or patients' anthropometric data.

The challenges associated with the use of administrative databases have been well documented. [16] In this study, the difficulties in selecting the patients with uncontrolled severe asthma were associated with potential measurement bias related to coding errors in hospital diagnoses; this source of error is likely limited and non-differential between groups. The algorithms assumed that filled prescriptions were proxies to treatment use; however, it is not possible to confirm that a filled prescription has been taken.

Potential indications of asthma treatments for other chronic pulmonary diseases such as COPD were accounted for, since an exclusion criterion based on ALD declarations or hospitalizations related to other chronic pulmonary diseases was considered. Despite this, some COPD patients may still have been included given the relatively old age of the asthmatic cohorts. This would have occurred if ALD for COPD has not been declared, or if a patient has

never been hospitalized during the last 5 years. Criterion requiring continuous insurance coverage may have resulted in a lower number of younger patients being included due to student-specific insurance offered during school years; however, the impact of this limit on the results is likely minimal.

Patients have been assigned to their group of interest (uncontrolled severe asthma, other patients with asthma, general population) at index date. Some patients may have evolved from non-asthma to asthma, or from asthma to uncontrolled severe asthma during follow-up and this was not considered in statistical analyses. However, given the duration of follow-up of two years, impact of such misclassification of patients during follow-up is probably limited.

The EGB offers the advantage of a limited number of patients lost to follow-up given the universal healthcare system present in France. It also has a few limits: while most patients were covered by the general scheme, patients covered by other plans may have not been selected due to the later integration of those plans in the EGB. Also, the algorithms used to define asthma and uncontrolled asthma excluded patients who died at the hospital around the time of index date, thereby potentially excluding the most severe and uncontrolled patients. Finally, additional residual confounding factors may persist despite the matching processes.

This large study allowing the comparison between patients with uncontrolled severe asthma and other patients with asthma and the general population, highlighted that severe asthma associated with non-control significantly affects mortality, healthcare use, and associated costs. This study emphasizes that close attention should be paid to ensure appropriate management of patients with severe asthma and monitoring of the level of control of asthma symptoms.

CONCLUSIONS

This database study demonstrates the huge burden of uncontrolled severe asthma in terms of mortality, morbidity, and healthcare resource consumption compared to other patients with asthma and the general population. These findings emphasize the importance of appropriate management in this high-risk population.

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Contributors All authors participated in the interpretation of the data, provided critical feedback and final approval for submission, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses. Stève Bénard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: all authors. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: de Larrard and Bénard. Critical revision of the manuscript for important intellectual content: Roche, Demoly, Garcia, Cancalon, Perez, Mahieu and Vieu. Statistical analysis: de Larrard, Bénard and Cancalon. Administrative, technical, or material support: Bénard, Perez, Mahieu and Vieu. Supervision: all authors.

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LIST OF FIGURE TITLES

Figure 1. RESONANCE study design

Figure 2. 24-month survival for the uncontrolled severe asthmatic cohort *vs.* general population and asthmatic control cohorts

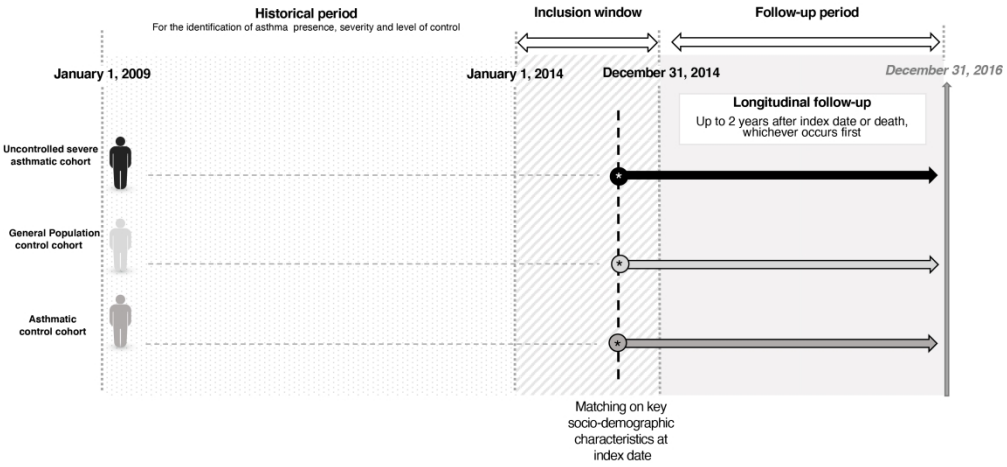

FIGURE 1. RESONANCE study design

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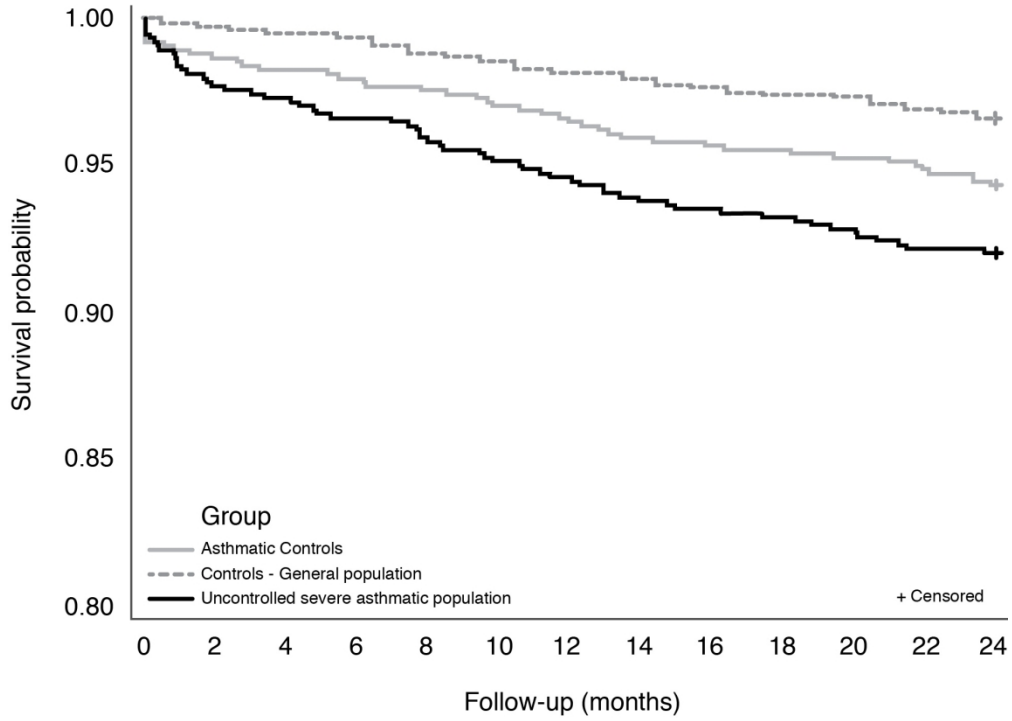

FIGURE 2. 24-month survival for the uncontrolled severe asthmatic cohort vs. general population and asthmatic control cohorts

166x119mm (300 x 300 DPI)

Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: findings from the retrospective observational RESONANCE study in France

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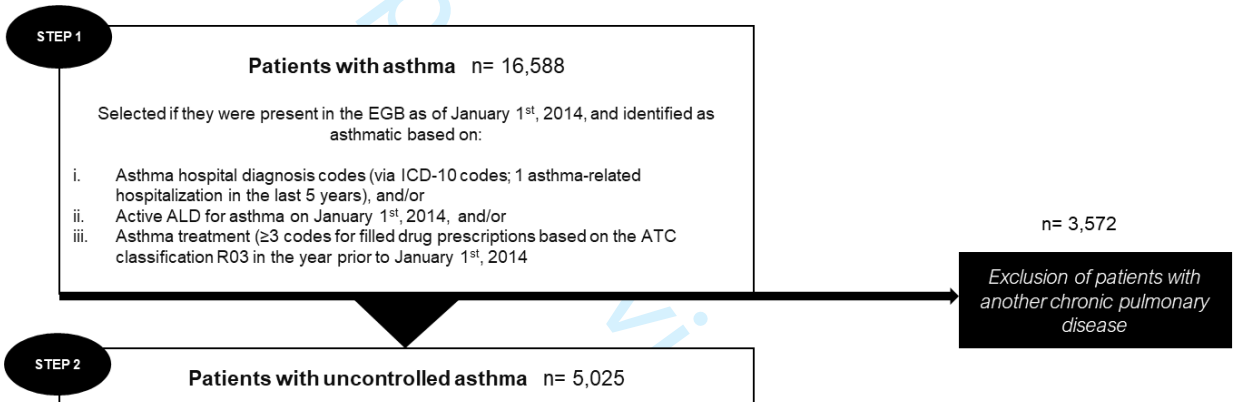
Supplementary materials

FIGURE S1. Patient selection algorithm

Key: ALD – affection de longue durée (long-term condition); ATC – Anatomical Therapeutic Chemical; COPD – chronic obstructive pulmonary disease; ICD-10 – International Classification of Diseases, 10th Revision; ICS – inhaled corticosteroid; LABA – long-acting ß2-agonist; LAMA – long-acting muscarinic antagonist; OCS – oral corticosteroid; SABA – short-acting ß2-agonist.



Footnote:
** Of note, these criteria did not apply to patients with an ALD other than asthma (i.e. rheumatoid arthritis, ulcerative colitis, Crohn's disease, cancer, etc) who can be treated by OCS identified by an exploratory analysis of ALD of patients from the target population meeting criterion.*

Methods – Additional details on drugs of interest

Asthma treatments:

- short-acting beta2-agonists (SABA),
- long-acting beta2-agonists (LABA),
- long-acting anticholinergics (LAMA),
- antileukotriene receptor antagonists (LTRA),
- xanthines,
- inhaled and oral corticosteroids (ICS and OCS),
- combination treatments.

Other drug classes of interest:

- nasal antihistamines,
- antihistamines,
- nonsteroidal anti-inflammatory drugs (NSAIDs),
- antibiotics,
- proton pump inhibitors (PPIs),
- psychotropic drugs,
- topical corticosteroids,
- topical immunosuppressants.

Methods – ICD-10 codes used

For Asthma definition

J45.0 Predominantly allergic asthma
J45.1 Non-allergic asthma
J45.8 Mixed asthma
J45.9 Asthma, Unspecified
J46 Status asthmaticus
J96 Respiratory failure, not elsewhere classified

For Other chronic pulmonary disease definition

J41 Simple and mucopurulent chronic bronchitis
J42 Unspecified chronic bronchitis
J43 Emphysema
J44 Other chronic obstructive pulmonary disease
J47 Bronchiectasis
J61 Pneumoconiosis due to asbestos and other mineral fiber
J62.8 Pneumoconiosis due to other dust containing silica
J68.0 Bronchitis due to chemicals, gases, fumes and vapors
E84 Mucoviscidosis
J92.0 Pleural plaque with presence of asbestos
J94.8 Other specified pleural conditions
J96.1+0 Insuffisance respiratoire chronique obstructive

Methods – Variables defined for propensity score matching

1. nasal corticosteroid (Yes/No)
2. systemic antihistamine (Yes/No)
3. non-steroidal anti-inflammatory drugs (Yes/No)
4. antibiotic (Yes/No)
5. proton pump inhibitor (Yes/No)
6. dermocorticoids (Yes/No)
7. psychotropic drug (Yes/No)
8. age (years)
9. number of outpatient consultations
10. charlson's score
11. consultation with a nurse (Yes/No)
12. cardio-vascular diseases (Yes/No)
13. ocular antihistamine (Yes/No)
14. hypertension (Yes/No)
15. osteoporosis (Yes/No)
16. number of consultations with a physiotherapist
17. consultations with a physiotherapist (Yes/No)
18. depression (Yes/No)
19. psychiatric illness (Yes/No)
20. number of emergency room visits
21. hospitalization (Yes/No)
22. number of consultations with a nurse
23. emergency room visits (Yes/No)
24. number of hospitalizations
25. nasal antihistamine (Yes/No)
26. cataract (Yes/No)
27. nasal polyposis (Yes/No)
28. number of hospital consultations
29. gastroesophageal reflux (Yes/No)
30. dyslipidemia (Yes/No)
31. arrhythmia (Yes/No)
32. hospital consultations (Yes/No)
33. cerebrovascular diseases (Yes/No)
34. anxiety (Yes/No)
35. rhinosinusitis (Yes/No)
36. heart failure (Yes/No)
37. diabetes (Yes/No)
38. coronary heart disease (Yes/No)
39. sex
40. psychotic disorders (Yes/No)
41. outpatient consultation (Yes/No)
42. topical immunosuppressant (Yes/No)
43. CMU (Yes/No)
44. myocardial infarction (Yes/No)
45. atopic dermatitis (Yes/No)

TABLE S1. Quality of direct matching between cohort of patients with uncontrolled severe asthma and general population

Matching variables	*Before Matching*			*After Matching*		
	Uncontrolled severe asthma cohort (n=739)	**General population (n=466,977)**	**Standardized mean differences**	**Uncontrolled severe asthma cohort (n=739)**	**General population (n=2,217)**	**Standardized mean differences***
Age (mean, SD)	62.0 (16.7)	48.5 (20.2)	0.7297	62.0 (16.7)	62.0 (16.7)	0.0000
Sex						
Male (n, %)	318 (43.0%)	228 841 (49.0%)	0.1201	318 (43.0%)	954 (43.0%)	0.0000
Female (n, %)	421 (57.0%)	238 136 (51.0%)		421 (57.0%)	1 263 (57.0%)	
Beneficiary of CMU-c (n, %)	74 (10.0%)	31 778 (6.8%)	0.1158	74 (10.0%)	222 (10.0%)	0.0000

* A standardized mean difference < 0,1 after matching is considered as acceptable.

TABLE S2. Quality of propensity score matching between cohort of patients with uncontrolled severe asthma and cohort of patients with asthma

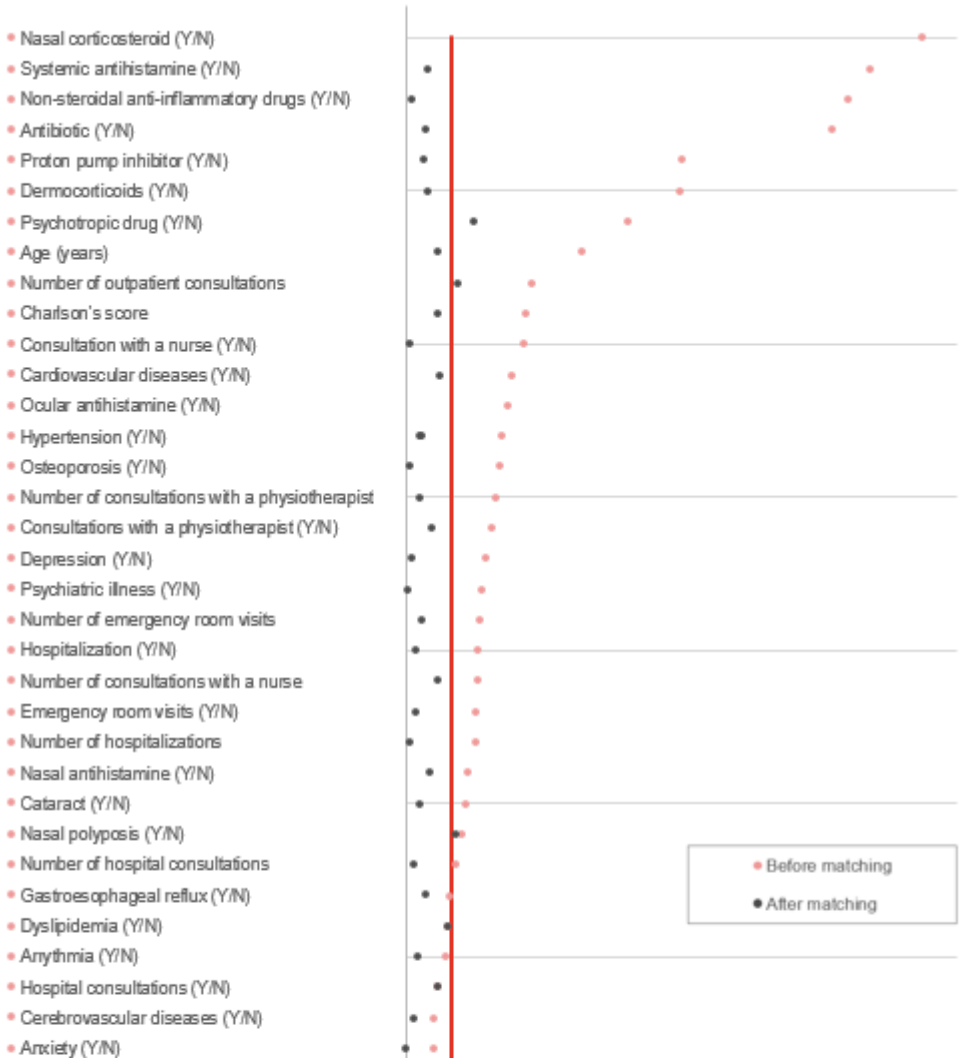
Matching variables	*Before Matching*			*After Matching*		
	Uncontrolled severe asthma cohort (n=739)	**Asthma cohort (n=15,849)**	**Standardized mean differences**	**Uncontrolled severe asthma cohort (n=739)**	**Asthma cohort (n=739)**	**Standardized mean differences***
Age (mean, SD)	62.0 (16.7)	54.8 (20.9)	0.3826	62.0 (16.7)	63.2 (17.2)	-0.0688
Sex						
Male (n, %)	318 (43.0%)	7 010 (44.2%)	0.0242	318 (43.0%)	347 (47.0%)	0.0789
Female (n, %)	421 (57.0%)	8 839 (55.8%)		421 (57.0%)	392 (53.0%)	
Beneficiary of CMU-c (n, %)	74 (10.0%)	1 536 (9.7%)	0.0108	74 (10.0%)	57 (7.7%)	0.0810
Cardiovascular diseases (n, %)	405 (54.8%)	6 863 (43.3%)	0.2316	405 (54.8%)	431 (58.3%)	-0.0710
Coronary heart disease (n, %)	55 (7.4%)	1 036 (6.5%)	0.0355	55 (7.4%)	69 (9.3%)	-0.0684
Myocardial infarction (n, %)	8 (1.1%)	179 (1.1%)	-0.0045	8 (1.1%)	8 (1.1%)	0.0000
Arrhythmia (n, %)	60 (8.1%)	946 (6.0%)	0.0841	60 (8.1%)	65 (8.8%)	-0.0243
Heart failure (n, %)	33 (4.5%)	527 (3.3%)	0.0590	33 (4.5%)	49 (6.6%)	-0.0947
Hypertension (n, %)	364 (49.3%)	6 178 (39.0%)	0.2081	364 (49.3%)	375 (50.7%)	-0.0298
Cerebrovascular diseases (n, %)	27 (3.7%)	411 (2.6%)	0.0610	27 (3.7%)	29 (3.9%)	-0.0142
Dyslipidemia (n, %)	237 (32.1%)	4 439 (28.0%)	0.0887	237 (32.1%)	268 (36.3%)	-0.0885
Diabetes (n, %)	108 (14.6%)	2 047 (12.9%)	0.0493	108 (14.6%)	112 (15.2%)	-0.0152
Osteoporosis (n, %)	110 (14.9%)	1 325 (8.4%)	0.2046	110 (14.9%)	112 (15.2%)	-0.0076
Psychiatric illness** (n, %)	224 (30.3%)	3 671 (23.2%)	0.1621	224 (30.3%)	223 (30.2%)	0.0029
Cataract (n, %)	75 (10.1%)	1 049 (6.6%)	0.1276	75 (10.1%)	69 (9.3%)	0.0274
Rhinosinusitis (n, %)	3 (0.4%)	17 (0.1%)	0.0591	3 (0.4%)	2 (0.3%)	0.0233
Gastroesophageal reflux (n, %)	79 (10.7%)	1 261 (8.0%)	0.0941	79 (10.7%)	69 (9.3%)	0.0451
Atopic dermatitis (n, %)	1 (0.1%)	22 (0.1%)	-0.0009	1 (0.1%)	0 (0.0%)	0.0521
Nasal polyposis (n, %)	14 (1.9%)	91 (0.6%)	0.1198	14 (1.9%)	5 (0.7%)	0.1083
Nasal antihistamine (n, %)	1 (0.1%)	197 (1.2%)	-0.1342	1 (0.1%)	3 (0.4%)	-0.0521
Ocular antihistamine (n, %)	4 (0.5%)	589 (3.7%)	-0.2213	4 (0.5%)	6 (0.8%)	-0.0330
Systemic antihistamine (n, %)	65 (8.8%)	7 892 (49.8%)	-1.0090	65 (8.8%)	75 (10.1%)	-0.0462
Nasal corticosteroid (n, %)	10 (1.4%)	6 597 (41.6%)	-1.1249	10 (1.4%)	15 (2.0%)	-0.0525

Non-steroidal anti-inflammatory drugs (n, %)	70 (9.5%)	7 756 (48.9%)	-0.9634	70 (9.5%)	73 (9.9%)	-0.0137
Antibiotic (n, %)	170 (23.0%)	10 249 (64.7%)	-0.9251	170 (23.0%)	184 (24.9%)	-0.0444
Proton pump inhibitor (n, %)	122 (16.5%)	6 776 (42.8%)	-0.6001	122 (16.5%)	132 (17.9%)	-0.0359
Psychotropic drug (n, %)	128 (17.3%)	6 091 (38.4%)	-0.4844	128 (17.3%)	172 (23.3%)	-0.1484
Dermocorticoids (n, %)	19 (2.6%)	3 321 (21.0%)	-0.5954	19 (2.6%)	25 (3.4%)	-0.0478
Topical immunosuppressant (n, %)	1 (0.1%)	31 (0.2%)	-0.0148	1 (0.1%)	0 (0.0%)	0.0521
Outpatient consultation (n, %)	656 (88.8%)	14 159 (89.3%)	-0.0182	656 (88.8%)	668 (90.4%)	-0.0532
Hospital consultation (n, %)	193 (26.1%)	3 685 (23.3%)	0.0665	193 (26.1%)	171 (23.1%)	0.0691
Consultation with a nurse (n, %)	551 (74.6%)	9 941 (62.7%)	0.2572	551 (74.6%)	548 (74.2%)	0.0093
Consultation with a physiotherapist (n, %)	383 (51.8%)	6 754 (42.6%)	0.1853	383 (51.8%)	363 (49.1%)	0.0541
Hospitalization (n, %)	468 (63.3%)	8 834 (55.7%)	0.1551	468 (63.3%)	475 (64.3%)	-0.0197
Emergency room visits (n, %)	356 (48.2%)	6 442 (40.6%)	0.1519	356 (48.2%)	349 (47.2%)	0.0190
Number of outpatient consultations (mean, SD)	36.9 (30.0)	29.2 (25.9)	0.2724	36.9 (30.0)	33.7 (26.7)	0.1128
Number of hospital consultations (mean, SD)	3.4 (10.2)	2.4 (7.9)	0.1094	3.4 (10.2)	3.3 (10.0)	0.0175
Number of consultations with a nurse (mean, SD)	53.5 (195.3)	27.9 (132.7)	0.1535	53.5 (195.3)	41.6 (162.1)	0.0665
Number of consultations with a physiotherapist (mean, SD)	37.0 (98.8)	21.1 (62.3)	0.1935	37.0 (98.8)	34.1 (104.0)	0.0286
Number of hospitalizations (mean, SD)	2,.3 (5.0)	1.6 (4.0)	0.1514	2.3 (5.0)	2.4 (5.0)	-0.0057
Number of emergency room visits (mean, SD)	1.2 (2.2)	0.9 (1.9)	0.1606	1.2 (2.2)	1.2 (1.9)	0.0340
Charlson's score (mean, SD)	3.6 (2.3)	3.0 (2.3)	0.2588	3.6 (2.3)	3.8 (2.4)	-0.0702

* A standardized mean difference < 0,1 after matching is considered as acceptable.

**Psychiatric illness includes depression, anxiety, and psychotic disorders.

FIGURE S2. Quality of propensity score matching between cohort of patients with uncontrolled severe asthma and cohort of patients with asthma



A standardized mean difference < 0,1 after matching is considered as acceptable.

FIGURE S3. Analysis of mortality by age group

Age group	Target population	Deceased target population	Asthmatic control cohort	Deceased asthmatic control cohort	RR	95% CI	RRR
[50;60[	140	6	135	1	5,79	[0,71;47,41]	-4,79
[60;70[	183	15	151	3	4,13	[1,22;13,97]	-3,13
[70;80[	136	14	161	10	1,66	[0,76;3,60]	-0,66
[80;90[	86	15	117	16	1,28	[0,68;2,41]	-0,28
≥90	28	9	21	12	0,56	[0,40;0,79]	0,44

Target population: Uncontrolled severe asthmatic cohort

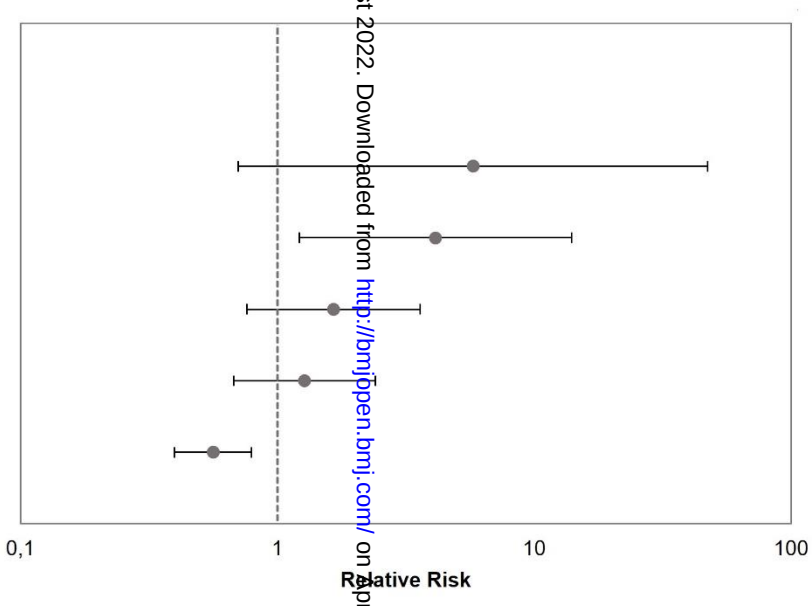
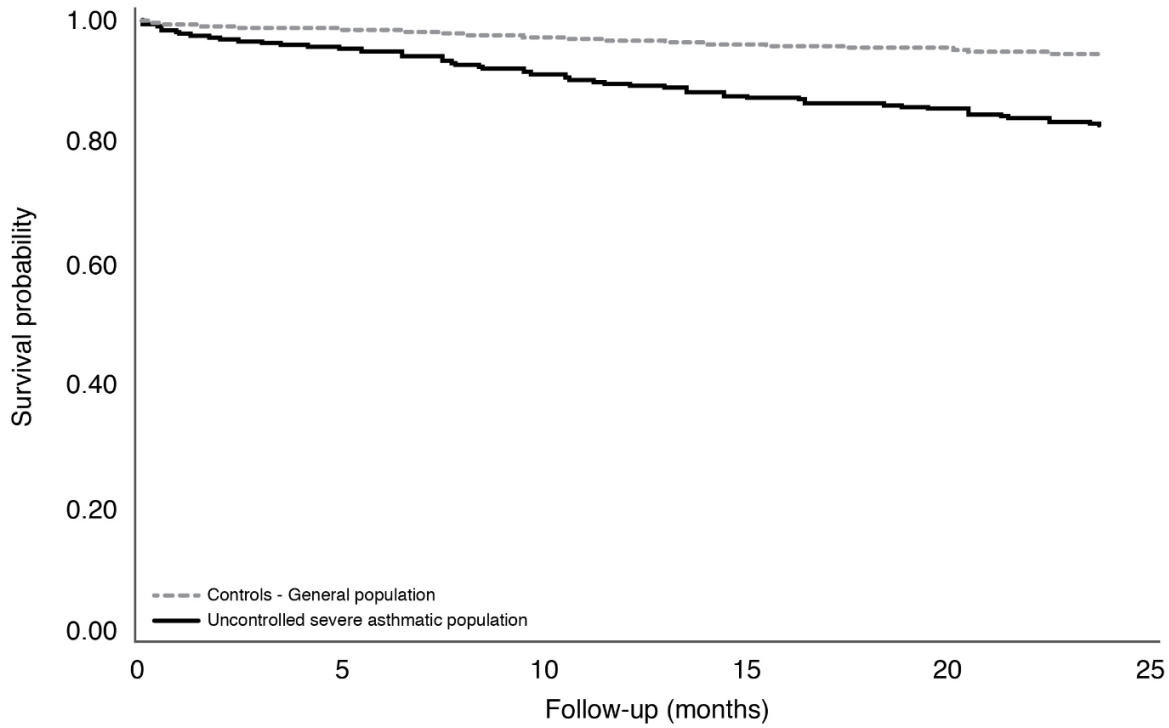


Table S3. Results of multivariate Cox model on mortality

Covariate	Hazard ratio	95% CI
Age (1-year increase)	1.07	1.05 - 1.09
History of cardiovascular diseases (with *vs.* without)	1.91	1.18 - 3.09
History of diabetes (with *vs.* without)	1.66	1.11 - 2.49
History of cancer (with *vs.* without)	2.40	1.64 - 3.50
Patients with uncontrolled severe asthma *vs.* general population in population with history of psychiatric disease	1.22	0.66 - 2.26
Patients with uncontrolled severe asthma *vs.* general population in population without history of psychiatric disease	3.25	2.14 - 4.92
History of psychiatric disease (with *vs*. without) in uncontrolled severe asthma cohort	0.93	0.52 – 1.65
History of psychiatric disease (with *vs*. without) in general population cohort	2.46	1.54 – 3.92

Key: CI – confidence interval.

FIGURE S4. 24-month survival for the uncontrolled severe asthmatic cohort versus general population among subjects without history of psychiatric disease



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7 (Figure S1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-16

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-16
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.