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Original Research

Asthma burden according to treatment steps in the French population-based cohort CONSTANCES

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ABSTRACT

Background: Data on health care consumption and costs of asthma in the French population are scarce.

Objectives: The study objective was to describe the burden of asthma according to GINA treatment steps in the CONSTANCES cohort.

Methods: Data from 162,725 participants included between 2012 and 2019 were extracted. Participants were considered as current asthmatics if asthma was reported at inclusion and asthma symptoms and/or treatments were reported in 2019. Participants were classified in three categories according to GINA treatment steps. The results were compared to non-asthmatic participants matched with a propensity score calculated on age, sex, region of residence, precariousness score and year of inclusion.

Results: Among 162,725 participants aged 18–69 years, 6783 asthmatics (1566 not treated for asthma, 2444 + 251 GINA steps 1 + 2, 1054 + 1315 GINA steps 3 + 4, and 153 GINA step 5) were matched with 6783 controls. Average annual ambulatory cost and average annual hospitalization cost were respectively €1925 and €719 for asthmatics versus €1376 and €511 for participants without asthma ($p < 0,0001$). Cardiovascular risk factors, comorbidities, visits and hospitalizations were higher for asthma participants as compared to controls and increased with GINA steps, as well as inpatient and outpatient costs. However, for cardiovascular risk factors and co-morbidities, differences were non-significant in multivariate analyses. Pharmacy costs were ten times higher for GINA step 5 participants than for GINA steps 1–2 participants: €3187 versus €393 ($p < 0,0001$).

Conclusion: mean cost of asthma was estimated at €757 per patient/year and increased with GINA treatment step.

1. Introduction

Asthma is a serious global health problem that affects an estimated 273 million persons worldwide [1] and may raise by 2025 with an additional 100 million subjects [2]. Reports on asthma prevalence and disease characterization have revealed wide variations within and between countries [3–7]; thus, assessing the burden of asthma can be challenging. In France, the prevalence of current asthma in 2018 was estimated between 6.4 and 9.3% depending on the definition and the study [8–10].

Notwithstanding that asthma-related hospitalizations and deaths have declined in some countries [11], the overall burden for patients from frequent exacerbations and day-to-day symptoms has augmented by almost 30% in the past 20 years [12]. The identification of comorbidities is essential to achieve an optimal control of asthma and is now an integral part of the management.

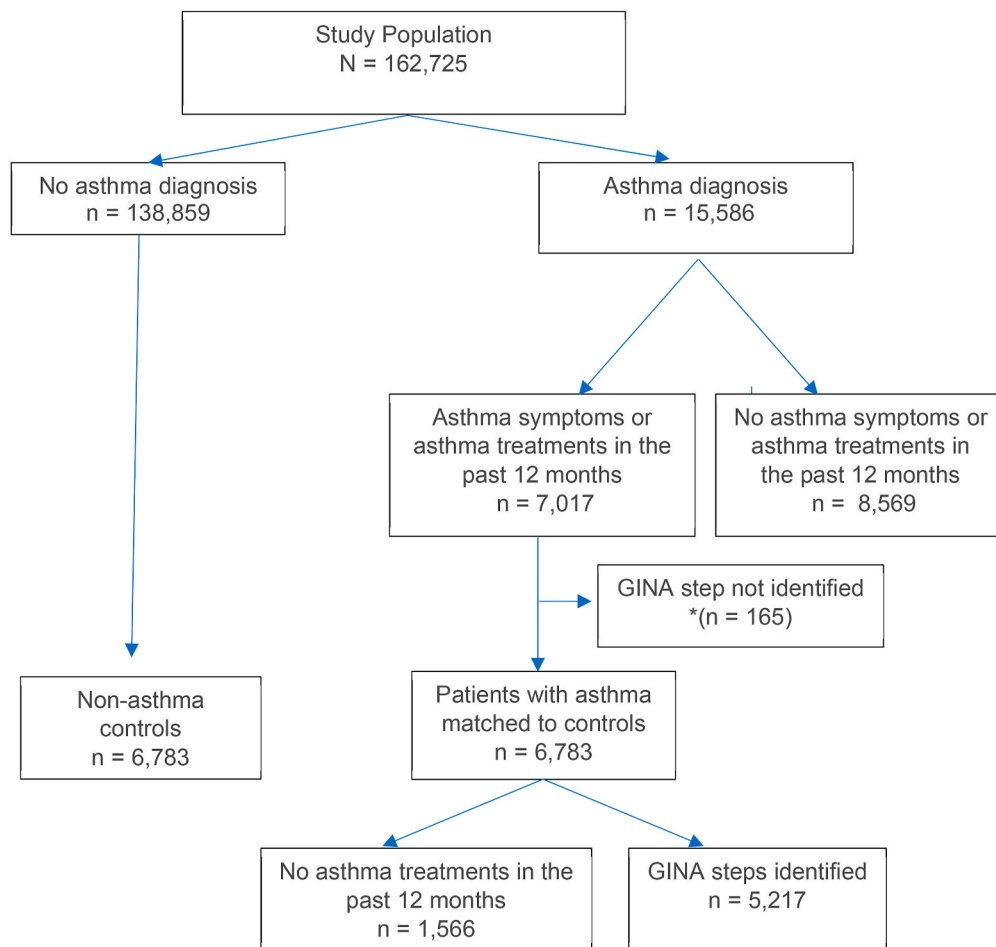
Despite the stability of asthma prevalence in France since 2006 [10], data on its economic burden are rare and old. The CONSTANCES cohort, which is a large sample of the general French adult population, offers the unique opportunity to better understand the economic and clinical burden of asthma in patients living with the disease.

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List of abbreviations			
ATS	American Thoracic Society	GINA	Global Initiative for Asthma
BMI	Body Mass Index	HPCS	Health Prevention Centres
CNIL	Commission Nationale de l'Informatique et des Libertés	ICS	inhaled corticosteroids
CNIS	Conseil National de l'Information Statistique	INSERM	Institutional Review Board of the National Institute for Medical Research
CNOM	National Medical Council (Conseil National de l'Ordre des Médecin)	LABA	long-acting beta agonist (LABA)
COBRA	Cohorte Obstruction Bronchique et Asthme	LAMA	long-acting muscarinic antagonist
EGB	échantillon généraliste des bénéficiaires	LTRA	Leukotriene receptor antagonists
ERS	European Respiratory Society	OCS	oral corticosteroids
FEV	Force Expiratory Volume	SABA	short-acting beta-agonist
FEV1	Forced expiratory volume in 1 s	SD	Standard deviation
		SNDS	French hospital and claims database
		USA:	Unites States of America



* the treatment for asthma could not be attributed to any GINA step

Fig. 1. Flowchart of study population.

The objectives of this study were to describe the healthcare burden in patients with asthma in France, in terms of symptoms, comorbidities, healthcare consumptions and related costs globally and according to GINA treatment steps.

2. Methods

We used data from the CONSTANCES cohort to identify participants

with current asthma and controls without ever-asthma. The CONSTANCES cohort is a randomly sample of 220,000 French adults aged 18–69 years at inception [13]. At inclusion, the selected participants were invited to fill out a self-administered questionnaire and undergo a comprehensive health examination at one of the participating Health Prevention Centres (HPCs). The follow-up includes an annual self-administered questionnaire, and a 4-year periodic visit to an HPC. Individual data is connected to the French hospital and claims database

(SNDS) which provides additional information.

2.1. This cohort study collects information from

- Case report forms completed by the physicians at the date of the participants inclusion in the cohort and at each 4-year periodic visit thereafter.
- Laboratory and other paraclinical tests including electrocardiogram and spirometry at inclusion and at 4-year periodic visits.
- Self-questionnaires filled out by the participants at inclusion and every year thereafter.
- Data collected from the French hospital and claims database (SNDS) that list all outpatient and inpatient healthcare consumptions.

Two groups of participants from the CONSTANCES cohort were selected to perform the present study:

1. Those diagnosed with asthma at inclusion who, in 2019 (when the respiratory questionnaire was filled in by all included participants), reported asthma symptoms or received a delivery of asthma drug in the past 12 months (current asthma).
2. Those with never asthma at inclusion, selected from the never-asthmatic group by 1:1 matching using a propensity score based on the following variables: age, gender, year at inclusion in the cohort, region of residence and EPICES score (Evaluation of Deprivation and Inequalities in Health Examination Centers²).

The index date was when each participant completed the asthma symptoms questionnaire in 2019.

For each eligible participant, information was extracted from the CONSTANCES cohort database on sociodemographic characteristics, cardiovascular risk factors, comorbidities documented by the physician at inclusion, paraclinical tests (eosinophil cells count, spirometry) performed at inclusion, health behavior (smoking and physical activities), healthcare consumptions in the year prior to the index date. Health resource consumptions and costs in the year prior to the index date were collected from the SNDS. For the calculation of the theoretical value of the FEV₁, the Global Lung function Initiative equations [14] were used.

Current asthmatics were classified according to GINA treatment steps (no treatment, Step 1–2, Step 3–4 and Step 5) based on drug treatments identified through the SNDS claims database.³ We considered drugs delivered in the past 3 months before the index date, except for short-acting beta agonists (SABA), for which we considered a delay of 18 months before the index date.

All statistical analyses were performed using SAS® software Version 9.4 (Cary, USA). Bivariate analyses were performed using Chi2 tests to assess qualitative variables with Yates continuity correction or Fisher's exact test for sample sizes less than 5. For quantitative variables, a Student's t-test or analysis of variance was performed when distribution was close to normal; otherwise, non-parametric tests including Wilcoxon and Kruskal-Wallis were used.

Within the asthmatic population, a logistic regression was performed to identify factors associated with comorbidities, risk factors and health behaviours across GINA step groups, adjusting for age, gender, socio-professional category, academic degree, marital status, income and the EPICES score.

Costs were calculated from a societal perspective.

The CONSTANCES Cohort project has obtained the authorization of the National Data Protection Authority on March 3, 2011 (Commission

² The EPICES score is directly available in the Constances database and is calculated with 11 questions related to social characteristics of the subjects.

³ GLOBAL INITIATIVE FOR ASTHMA. Global Strategy for Asthma Management and Prevention. Update August 2017. <http://ginasthma.org/download/317/>.

Table 1

Asthma treatments deliveries in the past 3 months (3 m) or 18 months (18 m) prior to inclusion.

	Step 1 and 2 N (%)	Step 3 and 4 N (%)	Step 5 N (%)	p-value
Population	2695*	2369*	153*	
ICS (3 m)	69 (2.6)	2369 (100.0)	146 (95.4)	<0.0001
LAMA (3 m)	--	117 (4.9)	111 (72.5)	<0.0001
LABA (3 m)	--	2084 (88.0)	142 (92.8)	<0.0001
LTRA (3 m)	181 (6.7)	370 (15.6)	54 (35.3)	<0.0001
Anti-IGE mAb (3 m)	--	--	17 (11.1)	<0.0001
OCS (3 m)	292 (10.8)	477 (20.1)	75 (49.0)	<0.0001
Continuous OCS (3 m)	--	--	43 (28.1)	<0.0001
SABA (3 m)	565 (21.0)	887 (37.4)	77 (50.3)	<0.0001
SABA (18 m)	2604 (96.6)	1590 (67.1)	124 (81.0)	<0.0001
Theophylline (3 m)	1 (0.0)	2 (0.1)	5 (3.3)	<0.0001
Participant treated for asthma (3 m) OR treated by SABA (18 m)	2695 (100.0)	2369 (100.0)	153 (100.0)	<0.0001

1566 participants had no treatment in the past 18 months and were not included in any treatment steps.

ICS: inhaled corticosteroids, OCS: oral corticosteroids, LAMA: long-acting muscarinic antagonist, LABA: long-acting beta-agonist, LTRA: Leukotriene receptor antagonists, SABA: short-acting beta-agonist, Anti-IGE mAb: anti-IGE monoclonal antibody.

Nationale de l'Informatique et des Libertés—CNIL, autorisation no.910486). CONSTANCES was approved by the National Council for Statistical Information (Conseil National de l'Information Statistique—CNIS), the National Medical Council (Conseil National de l'Ordre des Médecins—CNOM), and the Institutional Review Board of the National Institute for Medical Research-INSERM (authorisation no. 01–011). All participants signed a written informed consent.

3. Results

Fig. 1 depicts the flowchart of patients with asthma and never asthma controls. Among the 162,725 cohort participants at the time of data extraction, 15,586 (9.6%) were diagnosed with asthma by a physician at inclusion. About half (45%, n = 7017) reported asthma symptoms and/or had a claim for a drug delivery for asthma in the past 12 months prior to inclusion. Finally, 6783 patients with asthma were included in the analysis and matched with 6783 never asthma controls. The GINA treatment steps could be determined for 5217 patients who had deliveries of asthma drugs (the treatment scheme did not correspond to any GINA step for 165 patients and 1566 patients did not have any delivery of asthma treatments in the past 12 months).

Table I displays the proportions of patients with asthma who had an anti-asthma drug delivery in the past 3 months prior to the index date (18 months for SABA). As expected, higher proportions of asthmatics had a delivery of inhaled corticosteroids, long-acting beta-agonists, long-acting anti-muscarinic agents, oral corticosteroids, and leukotriene receptor antagonists in GINA steps 3–5.

Table III delineates the sociodemographic characteristics, results of paraclinical tests and health behaviors of patients with asthma and never asthma controls. The mean age of patients with asthma was 48.1 years, 55.4% were females, and 1096 (16.2%) had a full coverage for a severe chronic disease (asthma or another condition) in 2019 as compared to 794 never asthma controls (11.7%). A FEV₁/FVC ratio

Table 2
Sociodemographic characteristics, paraclinical tests and health behaviors.

	Never asthma controls N (%)	Asthma patients N (%)	p-value	Step 1 and 2 N (%)	Step 3 and 4 N (%)	Step 5 N (%)	p-value
Population	6783	6783	–	2695 ^a	2369 ^a	153 ^a	
Age at inclusion in the cohort CONSTANCES	44.6 (13.2)	45.2 (13.4)	0.02	42.3 (12.8)	49.0 (13.3)	56.4 (11.0)	<0.0001
18–29 years	609 (9.0%)	574 (8.5%)	0.07	515 (19.1%)	212 (8.9%)	5 (3.3%)	<0.0001
30–39 years	1625 (24.0%)	1617 (23.8%)		747 (27.7%)	452 (19.1%)	8 (5.2%)	
40–49 years	1734 (25.6%)	1639 (24.2%)		664 (24.6%)	530 (22.4%)	23 (15.0%)	
50–59 years	1275 (18.8%)	1276 (18.8%)		443 (16.4%)	524 (22.1%)	46 (30.1%)	
60–75 years	1540 (22.7%)	1677 (24.7%)		326 (12.1%)	651 (27.5%)	71 (46.4%)	
Sex							0.1678
Male	3001 (44.2)	3023 (44.6)	0.7038	1157 (42.9)	1087 (45.9)	71 (46.4)	
Female	3782 (55.8)	3760 (55.4)		1538 (57.1)	1282 (54.1)	82 (53.6)	
EPICES score (mean, SD)	15.3 (17.2)	16.5 (17.4)	<0.0001	16.2 (17.1)	17.2 (18.1)	25.6 (20.5)	<0.0001
Postgraduate degree	4113 (60.6)	4095 (60.4)	0.8000	1677 (62.2)	1293 (54.6)	42 (27.5)	<0.0001
Full reimbursement coverage for a long-term disease in 2019	794 (11.7%)	1096 (16.2)	<0.0001	340 (12.6)	495 (20.9)	98 (64.1)	<0.0001
Full reimbursement coverage for a long-term disease in 2019 with diagnosis of Asthma J45	–	200 (2.9)	<0.0001	35 (1.3)	121 (5.1)	36 (23.5)	<0.0001
FEV1/FVC ratio	NA = 1676	NA = 1606		NA = 601	NA = 611	NA = 57	
<70%	230 (4.5)	975 (18.8)	<0.0001	289 (13.8)	469 (26.7)	46 (47.9)	<0.0001
≥70%	4877 (95.5)	4202 (81.2)		1805 (86.2)	1289 (73.3)	50 (52.1)	
Predicted FEV1%	NA = 1676	NA = 1587		NA = 594	NA = 607	NA = 55	<0.0001
<80%	230 (4.5)	1084 (20.9)	<0.0001	357 (17.0)	490 (27.8)	49 (50.0)	
≥ 80%	4877 (95.5)	4112 (79.1)		1744 (83.0)	1272 (72.2)	49 (50.0)	
Blood eosinophil count	NA = 323	NA = 264		NA = 107	NA = 76	NA = 10	<0.0001
<150/mm3	3365 (52.1)	1849 (28.4)		738 (28.5)	594 (25.9)	27 (18.9)	
150-300/mm3	2307 (35.7)	2589 (39.7)	<0.0001	1047 (40.5)	879 (38.3)	70 (49.0)	
>300/mm3	788 (12.2)	2081 (31.9)		803 (31.0)	820 (35.8)	46 (32.2)	
Body Mass Index (BMI)	NA = 82	NA = 75	<0.0001	NA = 29	NA = 29	NA = 2	<0.0001
<18.5	200 (3.0)	170 (2.5)		72 (2.7)	51 (2.2)	2 (1.3)	
[18.5–25[3798 (56.7)	3267 (48.7)		1377 (51.7)	1011 (43.2)	41 (27.2)	
[25–30[1957 (29.2)	2166 (32.3)		806 (30.2)	829 (35.4)	65 (43.0)	
More than 30	746 (11.1)	1105 (16.5)		411 (15.4)	449 (19.2)	43 (28.5)	
Smoker status							<0.0001
Current smoker	1264 (18.6)	1208 (17.8)		519 (19.3)	413 (17.4)	22 (14.4)	
Ex-smoker	2235 (33.0)	2366 (34.9)	0.053	882 (32.7)	908 (38.3)	62 (40.5)	
Never smoker	3.284 (48.4)	3209 (47.3)		1294 (48.0)	1048 (44.2)	69 (45.1)	

FEV (Forced Expiratory Volume) in 1 s and FVC (Forced Vital Capacity).

^a 1566 participants had no treatment in the past 18 months and were not included in any treatment steps; NA: no answer.

<70% and a predicted FEV1 < 80% were respectively reported for 18.8% and 20.9% of patients with asthma compared to 4.5% and 4.5% for the never asthma group. A blood eosinophil count >300/mm³ was documented for 31.9% of patients with asthma and 12.2% of never asthma controls. More patients with asthma had a BMI >30 compared to never asthma controls. The proportions of current and ex-smokers were similar in both groups. Mean age at inclusion, proportions of participants with an altered pulmonary function and a blood eosinophil count >150/mm³ increased with GINA steps. The socioeconomic status of patients with asthma deteriorated with higher GINA steps as shown by increased EPICES score. In addition, the proportion of participants with a postgraduate degree decreased from step 1–2 to step 5. Finally, the proportion of patients with a BMI >30 increased from step 1–2 to step 5.

Several comorbidities (hypertension, hypercholesterolemia, type 2 diabetes, ischemic coronary heart disease, chronic bronchitis/

emphysema, depression, and suicide attempt) were significantly more frequent among patients with asthma (Table II). These frequencies significantly increased with GINA steps; however, the differences decreased and became non-significant after adjustment for potential confounding factors (age, gender, socio-professional category, academic degree, marital status, income, EPICES score) (Fig. 2).

Table IV delineates healthcare consumptions in the year prior to inclusion. Asthmatics were more often hospitalized (23.0% vs 18.1%) and had at least one consultation with a lung specialist (20.4% vs 3.1%), a general practitioner or a nurse compared to controls. Among asthmatics, 22.0% had at least one spirometry testing. Importantly, healthcare consumptions increased gradually with the GINA steps (Table IV).

Table V illustrates the costs of healthcare consumptions from a societal perspective. The overall cost of healthcare consumptions for asthmatics was estimated at €2,644, versus €1886 for the control group,

Table 3
Comorbidities identified at inclusion in the cohort.

Population	Controls n (%)	Asthmatics n (%)	p-value	Step 1 and 2 n (%)	Step 3 and 4 n (%)	Step 5 n (%)	p-value
	6783	6783		2695 ^a	2369 ^a	153 ^a	
Hypertension	NA = 8	NA = 32	<0.0001	NA = 11	NA = 12	- -	<0.0001
Yes	618 (9.1)	805 (11.9)		233 (8.7)	383 (16.2)	42 (27.5)	
No	6157 (90.9)	5946 (88.1)		2451 (91.3)	1974 (83.8)	111 (72.5)	
Hypercholesterolemia	NA = 44	NA = 58	0.0219	NA = 21	NA = 20	NA = 2	<0.0001
Yes	455 (6.8)	523 (7.8)		156 (5.8)	238 (10.1)	34 (22.5)	
No	6284 (93.2)	6202 (92.2)		2518 (94.2)	2111 (89.9)	117 (77.5)	
Type II diabetes	NA = 46	NA = 53	0.0013	NA = 20	NA = 19	NA = 1	<0.0001
Yes	98 (1.5)	148 (2.2)		46 (1.7)	67 (2.9)	12 (7.9)	
No	6639 (98.5)	6582 (97.8)		2629 (98.3)	2283 (97.1)	140 (92.1)	
Coronary Heart Disease ^a	NA = 14	NA = 52	0.0018	NA = 17	NA = 23	NA = 1	0.0189
Yes	27 (0.4)	55 (0.8)		16 (0.6)	28 (1.2)	3 (2.0)	
No	6742 (99.6)	6676 (99.2)		2662 (99.4)	2318 (98.8)	149 (98.0)	
Chronic bronchitis	NA = 9	NA = 314	<0.0001	NA = 124	NA = 121	NA = 11	<0.0001
Yes	25 (0.4)	161 (2.5)		32 (1.2)	85 (3.8)	32 (22.5)	
No	6749 (99.6)	6308 (97.5)		2539 (98.8)	2163 (96.2)	110 (77.5)	
Emphysema	NA = 1164	NA = 1437	0.0349	NA = 514	NA = 550	NA = 46	0.0023
Yes	16 (0.3)	29 (0.5)		11 (0.5)	13 (0.7)	3 (2.8)	
No	5603 (99.7)	5317 (99.5)		2170 (99.5)	1806 (99.3)	104 (97.2)	
Depression	NA = 21	NA = 26	<0.0001	NA = 6	NA = 10	- -	0.0293
Yes	956 (14.1)	1324 (19.6)		496 (18.4)	495 (21.0)	39 (25.5)	
No	5806 (85.9)	5433 (80.4)		2193 (81.6)	1864 (79.0)	114 (74.5)	
Past suicide attempt	NA = 57	NA = 84	<0.0001	NA = 33	NA = 32	NA = 1	0.8634
Yes	134 (2.0)	226 (3.4)		89 (3.3)	83 (3.6)	6 (3.9)	
No	6592 (98.0)	6473 (96.6)		2573 (96.7)	2254 (96.4)	146 (96.1)	
Depression Score (CEDs Scale at inclusion) ^b	10.8 (8.9)	12.0 (9.7)	<0.0001	11.9 (9.5)	12.0 (9.8)	14.8 (10.5)	0.0076
Depression status (CEDs scale)	NA = 292	NA = 313	<0.0001	NA = 113	NA = 118	NA = 19	0.0010
Not Depressive	5036 (77.6)	4699 (72.6)		1906 (73.8)	1635 (72.6)	78 (58.2)	
Depressive	1455 (22.4)	1771 (27.4)		676 (26.2)	616 (27.4)	56 (41.8)	

^a Angina pectoris and/or history of myocardial infarction.

^b Mean (SD); * 1566 participants had no treatment in the past 18 months and were not included in any treatment steps; NA: no answer.

which corresponds to an incremental cost of €758 including €208 for hospital and €550 for ambulatory costs. For ambulatory consumptions, the incremental cost was higher for pharmacy (€272), medical consultations and visits (€139), and medical devices (€50). Cost of healthcare consumptions increased with the GINA steps from €2279 for step 1–2 to €3106 for steps 3–4 and €8593 for step 5. This increase was related to both hospitalizations (respectively €633, €810 and €2340) and ambulatory care (€1,646, €2296 and €6252).

4. Discussion

In this observational study conducted in France using the CONSTANCES general population cohort, we investigated the healthcare burden in 6783 asthmatics matched with controls in a 1:1 ratio. Most of the asthmatics were managed using GINA step 1–2 (2695) and step 3–4 (2369) treatments, only very few (153) receiving GINA step 5 treatment. Except for chronic bronchitis, comorbid conditions were not more frequent in asthmatics compared to controls after adjusting for confounding factors such as age, gender, socio-professional category, academic degree, income, and EPICES score. The overall cost of healthcare consumptions for asthmatics was estimated at €2,644, versus €1886 for the control group, which corresponds to an incremental cost of €758.

Constances is the largest French population-based epidemiological study in adults. Constances is however not fully representative of the French adult population as 1) participants were randomly selected from the beneficiaries of the National Health Insurance Fund (“Caisse nationale d’assurance maladie”, CNAM) that covered around 85% of the French population, and 2) some geographical areas of France were not included. Nevertheless, the prevalence of asthma in our study is consistent with what was previously reported. As all consumptions for asthma were captured in the claims database, we were able to

extensively characterize our studied patient population. Some limitations of the study should also be acknowledged. We used GINA treatment steps to approach asthma severity. Although GINA step is a well-established criterion, it is an indirect proxy for asthma severity. Limited conclusions can be drawn from the GINA step 5 given the low number of patients in that step. Furthermore, the treatment steps were missing for some patients and could not be reconstituted. Since we investigated only direct costs, no data on indirect costs could be reported including work-related losses and early mortality. Finally, the use of a propensity score to select the control population without asthma does not completely eliminate the risk of imbalance between studied population.

Although comorbid conditions have been increasingly reported as contributors to poor asthma control, their role in the clinical expression of the disease has yet to be fully elucidated [15]. In our study, we observed a higher proportion of asthma patients who received ICS in GINA step 3–4 (100%) and GINA step 5 (95.4%) compared to patients with a delivery of SABA for GINA step 3–4 (37.4%) and GINA step 5 (81%) in the past 3 months. We found higher prevalences of comorbid conditions among patients with asthma, however, the differences decreased and became non-significant after adjustment. It is important to note that asthmatics from the CONSTANCES cohort are identified in a sample of the general population accepting to undergo a complete health check-up. As such it may be hypothesized that they are “less sick” than asthmatics from asthma cohorts, which could impact the rate of comorbidities. Unfortunately, we have no way of exploring this hypothesis. Several studies have reported an increased prevalence of comorbidities due to systemic corticosteroid use in patients with asthma, ranging from psychological effects to serious and life-threatening conditions including type 2 diabetes, cardiovascular diseases, obesity, sleep disturbance, fractures, cataracts, and adrenal

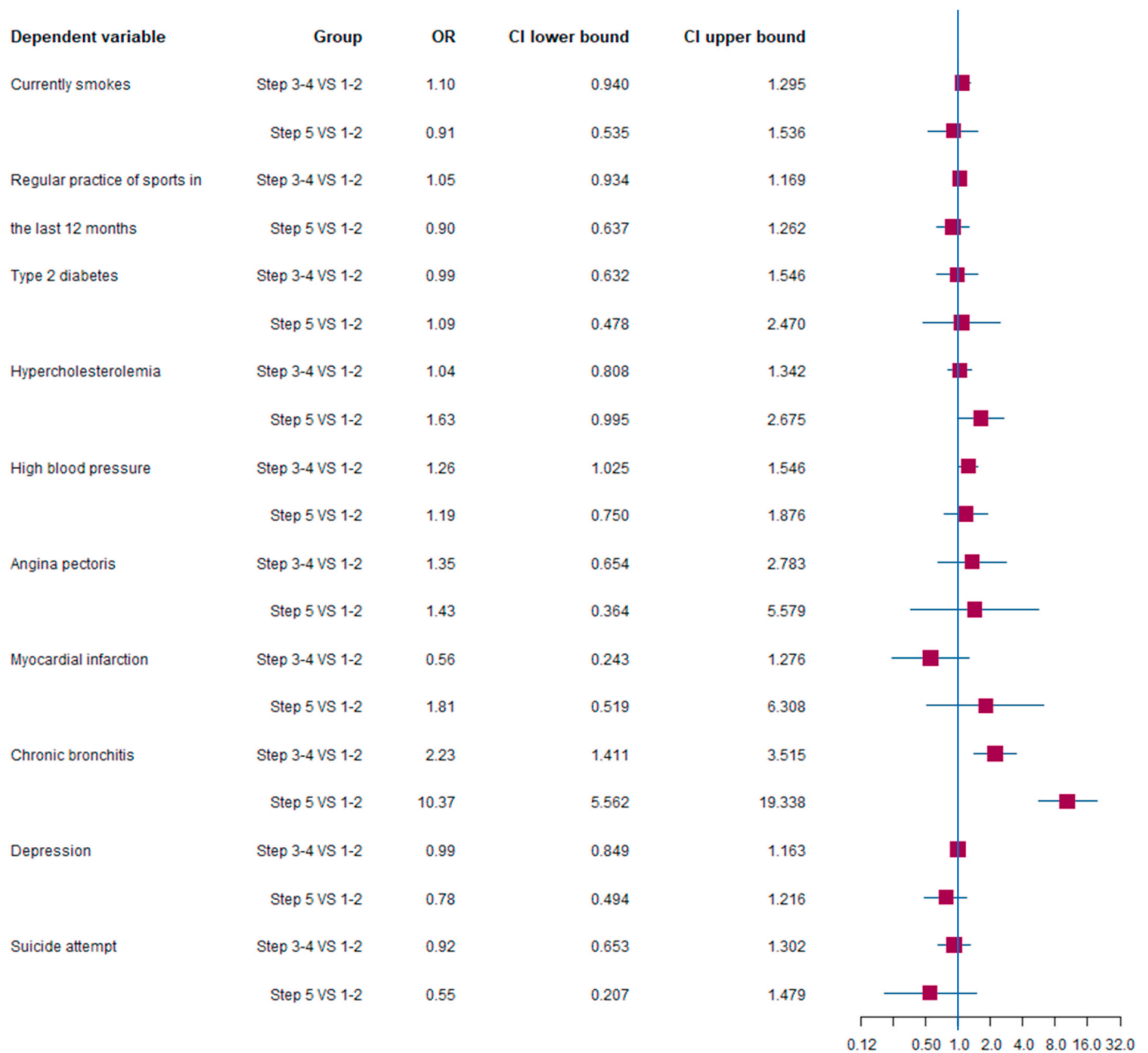


Fig. 2. Multivariate analysis on comorbidities, risk factors, and health behaviors in patients with asthma vs never asthma controls; odds ratio adjusted for age, gender, socio-professional category, academic degree, marital status income, and EPICES score.

Table 4
Healthcare consumptions in the year prior to inclusion.

	Never asthma controls N (%)	Asthma patients N (%)	p-value	Step 1 and 2 N (%)	Step 3 and 4 N (%)	Step 5 N (%)	p-value
Population	6783	6783	<0.0001	2695 ^a	2369 ^a	153 ^a	<0.0001
Hospitalization	1229 (18.1)	1557 (23.0)	<0.0001	577 (21.4)	608 (25.7)	70 (45.8)	<0.0001
≥1 consultation with a general practitioner ^b	5722 (84.4)	6306 (93.0)	<0.0001	2556 (94.8)	2295 (96.9)	151 (98.7)	<0.0001
≥1 consultation with a specialist ^b	4328 (63.8)	4946 (72.9)	<0.0001	1899 (70.5)	1877 (79.2)	143 (93.5)	<0.0001
≥1 consultation with a lung specialist ^b	212 (3.1)	1383 (20.4)	<0.0001	352 (13.1)	768 (32.4)	108 (70.6)	<0.0001
≥1 outpatient consultation	1039 (15.3)	1338 (19.7)	<0.0001	510 (18.9)	507 (21.4)	63 (41.2)	<0.0001
≥1 consultation with a nurse	2263 (33.4)	2668 (39.3)	<0.0001	965 (35.8)	1061 (44.8)	109 (71.2)	<0.0001
≥1 spirometry	–	1493 (22.0)	<0.0001	413 (15.3)	819 (34.6)	103 (67.3)	<0.0001

All differences between subgroups were statistically significant (p < 0.0001).

^a 1566 participants had no treatment in the past 18 months and were not included in any treatment steps.

^b Outpatient consultations with physicians in public hospitals were not collected.

Table 5
Costs of Healthcare consumptions.

Population	Never asthma controls N (%)	Asthma patients N (%)	p-value	Step 1 and 2	Step 3 and 4	Step 5	p-value
	6783	6783		2695 ^a	2369 ^a	153 ^a	
Costs, € (mean, SD)							
Medical fees	470.2 (646.6)	609.1 (744.0)	<0.0001	574.2 (720.3)	685.3 (735.8)	1237.6 (1315.3)	<0.0001
Dentist	140.1 (416.6)	150.7 (446.0)	0.0020	137.6 (415.8)	171.8 (474.1)	249.7 (785.4)	<0.0001
Pharmacy	296.0 (1270.3)	567.9 (1448.6)	<0.0001	393.5 (1116.3)	763.8 (1427.9)	3187.1 (4686.8)	<0.0001
Laboratory	81.6 (157.2)	96.4 (158.1)	<0.0001	92.3 (156.1)	98.8 (146.9)	227.6 (270.2)	<0.0001
Paramedics	100.6 (275.6)	139.6 (342.8)	<0.0001	128.1 (313.4)	153.8 (361.9)	383.6 (710.4)	<0.0001
Medical devices	223.8 (503.4)	273.7 (584.1)	<0.0001	240.8 (502.6)	323.4 (644.0)	673.8 (1211.0)	<0.0001
Transports	16.5 (164.8)	26.8 (237.4)	<0.0001	20.8 (197.5)	33.2 (275.0)	133.2 (499.5)	<0.0001
Other costs	46.8 (459.8)	61.2 (408.0)	<0.0001	59.4 (478.8)	66.3 (375.3)	159.8 (429.2)	<0.0001
Total cost of ambulatory care	1375.6 (2107.6)	1925.3 (2475.3)	<0.0001	1646.7 (2196.4)	2296.3 (2418.5)	6252.4 (5916.9)	<0.0001
Total cost of hospitalisations	511.0 (2425.0)	719.4 (3115.3)	<0.0001	633.1 (2860.4)	810.4 (3354.3)	2340.8 (5457.9)	<0.0001
Total cost	1886.6 (3777.8)	2644.7 (4736.8)	<0.0001	2279.8 (4430.6)	3106.7 (4861.2)	8593.2 (8962.4)	<0.0001

^a 1566 participants had no treatment in the past 18 months and were not included in any treatment steps, SD: Standard Deviation.

suppression [17–23].

Since 2020, the GINA document recommends low-dose ICS–formoterol as the preferred symptom reliever at any treatment step or SABA as an alternative (GINA), which is based on two concerns: first, SABA-only treatment (as a treatment option for step 1) increases urgent asthma-related healthcare [24]. Second, although low daily dose of ICS (as a treatment option for step 2) is highly effective in reducing asthma symptoms, adherence to ICS remains challenging for most patients which expose them to the risk of SABA-only treatment [16]. In our population, we found that most asthmatics (96.6%) received a SABA to manage their symptoms in GINA step 1 and 2 compared to only 2.6% who had a delivery of ICS. This result is in line with the absence of indication of low-dose ICS–formoterol for GINA step 1 and 2 in Europe. Beyond the description of delivered treatments it would be of interest to analyse patients' adherence to these medications, to better understand the burden of disease and the possible determinants associated with poor adherence. This could be further explored in future studies in the Constances cohort. It would also be of interest to explore whether patients' care differ according to the type of geographic area such as urban versus rural or other indicators for socioeconomic disadvantaged regions.

Not surprisingly, we found that healthcare consumption was higher in asthmatics compared to controls and significantly increased with the GINA steps, which is consistent with previous studies [25–27]. We estimated the incremental cost to be €758 for healthcare consumption in patients with asthma, largely driven by pharmacy costs and medical fees, but also hospitalizations. All healthcare consumption costs increased with the GINA steps. It is possible that a part of these costs are related to comorbidities associated with asthma as we did not adjust the cost estimates on comorbidities, in line with the study objective to capture crude healthcare costs, considering that costs related to asthma comorbidities are part of the global burden of asthma. Other cohorts and registries were actually designed in the same manner [29] or even without any control group [30]. Our findings are consistent with that of Jacob et al. [28] in Germany who reported a €753 higher total cost per patient with asthma compared to the control group. In a review on the costs and social impact of asthma in several European countries, Nunes et al. [7] estimated the annual direct and indirect per capita costs to reach \$2000 (\$2496 in 2012) in France, Italy, and Norway. We observed the highest cost in GINA step 5, accounting for €8593 which is similar to previous studies conducted in France [29,30]. More specifically, Bourdin et al. [29] used the permanent beneficiaries sample database (EGB) in France and reported an absolute cost of severe asthma at \$9227.

Finally, it is important to note that we observed a relatively low use of spirometry and specialist visits in patients with GINA steps 3–4 (30–35% of patients with spirometry and/or pulmonologist visit) and

GINA step 5 (approximately 70% for each) therapy. Improving care pathways for these patients could improve outcomes.

In conclusion, the findings of this study shed light on the substantial burden of asthma in terms of comorbidities and healthcare consumptions in France. This burden increases notably with GINA treatment steps. This highlights the need for a broader paradigm of asthma management including larger access to asthma education and more elaborated care pathways (spirometry and/or pulmonologist visits) that could help control symptoms, reduce OCS use and costs.

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CRediT authorship contribution statement

Nicolas Roche: Writing – original draft, participated in the study design and the interpretation of the study results, participated in the writing of the manuscript. **Rachel Nadif:** Writing – original draft, participated in the study design and the interpretation of the study results, participated in the writing of the manuscript. **Caroline Fabry-Vendrand:** Writing – original draft, participated in the study design and the interpretation of the study results, participated in the writing of the manuscript. **Laura Pillot:** Writing – original draft, participated in the writing of the manuscript. **Gabriel Thabut:** Writing – original draft, participated in the writing of the manuscript. **C. Teissier:** Formal analysis, performed the statistical analysis. **Stéphane Bouée:** Writing – original draft, Formal analysis, participated in the study design and the interpretation of the study results, performed the statistical analysis, participated in the writing of the manuscript. **Marcel Goldberg:** Writing – original draft, participated in the study design and the interpretation of the study results, participated in the writing of the manuscript. **Marie Zins:** Writing – original draft, participated in the study design and the interpretation of the study results, participated in the writing of the manuscript.

Declaration of competing interest

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Goldberg and Marie Zins have no links of interest.

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