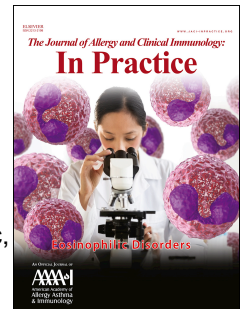


Accepted Manuscript

Changes in persistent asthma care and outcomes from 2006 to 2016 in France

Manon Belhassen, PhD, Maëva Nolin, MSc, Anjan Nibber, PhD, Marine Ginoux, MSc, Gilles Devouassoux, MD, PhD, Eric van Ganse, MD, PhD



PII: S2213-2198(19)30202-8

DOI: <https://doi.org/10.1016/j.jaip.2019.02.025>

Reference: JAIP 2129

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 10 September 2018

Revised Date: 15 February 2019

Accepted Date: 15 February 2019

Please cite this article as: Belhassen M, Nolin M, Nibber A, Ginoux M, Devouassoux G, van Ganse E, Changes in persistent asthma care and outcomes from 2006 to 2016 in France, *The Journal of Allergy and Clinical Immunology: In Practice* (2019), doi: <https://doi.org/10.1016/j.jaip.2019.02.025>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Changes in persistent asthma care and outcomes from 2006 to 2016 in France

Manon BELHASSEN¹ PhD, Maëva NOLIN¹ MSc, Anjan NIBBER² PhD, Marine GINOUX¹ MSc, Gilles DEVOUASSOUX³ MD, PhD, Eric VAN GANSE^{1,3,4} MD, PhD

¹ PELyon, PharmacoEpidemiology Lyon, Lyon, France

² University of Oxford Medical School, Oxford, UK

³ Respiratory Medicine, Croix Rousse University Hospital, and EA7426 University Claude Bernard Lyon-1, Lyon, France

⁴ HESPER 7425, Health Services and Performance Research, University Claude Bernard Lyon 1, Lyon, France

Corresponding author and reprint requests:

Manon Belhassen, PhD

PELyon

Faculté d'Odontologie

11 rue Guillaume Paradin

69008 Lyon

France.

Email: manon.belhassen@univ-lyon1.fr

Tel: +33 (0) 478 785 701,

Fax: +33 (0) 478 778 660

Word count: 3,434 words, 37 references, 6 Tables and/or figures

Short title: **Asthma care between 2006 and 2016**

Declaration of interests:

Eric Van Ganse reports grants and personal fees from ALK ABELLO, grants and personal fees from Bayer, grants and personal fees from BMS, grants and personal fees from GlaxoSmithKline, grants and personal fees from Merck Sharp and Dohme, personal fees from PELyon, outside the submitted work. Gilles Devouassoux has received speaker honorarium from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Merck Sharpe & Dohme, and Takeda, and consultancy from Novartis and Merck Sharpe & Dohme, outside the submitted work. Manon Belhassen, Marine Ginoux, Anjan Nibber, and Maeva Nolin have nothing to disclose.

ABSTRACT (max 250 words)

Background: Changes in asthma care need to be documented at arrival of biotherapies.

Objectives: To characterize changes in asthma care and outcomes in patients with persistent asthma.

Methods: Repeated transversal analyses were conducted on a historical cohort using the French national claims data over 10 years. Patients aged 18-40 years with either ≥ 1 (any use [AU] population) or ≥ 4 yearly dispensings (high use [HU] population) of controller therapy were selected. Clinical and demographic features were characterized, and comparisons were made between 2006 and 2016 to assess temporal changes in asthma therapy, healthcare resource utilization, and outcomes.

Results: In 2016, prevalent use of controller therapy was 5.2% (AUP) and 0.8% (HUP) of the population aged 18-40 years. In the AU population, the use of long-acting β -agonists (LABA) in monotherapy, and inhaled corticosteroids (ICS) decreased (1.7 and 40.3% in 2016, respectively), whereas the use of fixed-dose combinations (FDCs) increased (56.4%). In both populations, visits to respiratory or hospital physicians and pulmonary function testing increased with time, in parallel to a decreasing number of general practitioner visits; in addition, oral corticosteroids (OCS) use, and incidence of emergency room (ER) visits increased. However, asthma hospitalizations and mortality remained low in both populations.

Conclusion: Changes in persistent asthma care included replacement of ICS by FDCs, decreased use of LABAs as a monotherapy, and increased involvement of secondary care physicians. In parallel, despite low figures for hospital admissions and mortality, overall use of OCS and incidence of ER visits have increased over the last decade.

69

70 What is already known about this topic?

71 Few studies have investigated with valid data trends in asthma management in the general population.

72

73 What does this article add to our knowledge?

74 Prevalence of persistent asthma remained stable; changes included raised involvement of secondary
75 care at the expense of primary care, as well as an increased use of oral corticosteroids and incidence of
76 emergency room visits.

77

78 How does this study impact current management guidelines?

79 Present data suggest inappropriate implementation of asthma management guidelines in France.
80 Continuity of care should be encouraged between primary and secondary care, in parallel to increased
81 support to self-management.

82

83

84

85

86 Key words: **asthma, care, claims data, outcomes**

87

List of abbreviations

88	
89	
90	ATC: Anatomical Therapeutic Classification
91	AUP: “any use” population
92	COPD: Chronic Obstructive Pulmonary Disease
93	EGB: Echantillon Généraliste de Bénéficiaires (General Sample of Beneficiaries)
94	ER: Emergency Room
95	FDC: Fixed-Dose Combination
96	GP: General Practitioner
97	HUP: “high use” population
98	ICS: Inhaled Corticosteroids
99	LABA: Long-Acting β 2-Agonist
100	LTD: Long-Term Disease
101	LTRA: Leukotriene Receptor Antagonist
102	OCS: Oral Corticosteroids
103	PFT: Pulmonary Function Testing
104	SABA: Short-Acting β 2 Agonists
105	

BACKGROUND

Asthma is a common chronic respiratory condition affecting approximately 300 million children and adults worldwide. Over 250,000 annual deaths are attributed to the disease, many of which are preventable. Mortality rates are highest in countries where access to controller therapy is lacking (1). Despite widely disseminated guidelines for asthma management (2, 3), there has been no recent change in global asthma mortality rates, except in Eastern Europe, Western Europe and East Asia, where a downward trend has been observed (4). Asthma remains a pivotal public health issue, mainly as a consequence of poor overall disease control (5, 6). Factors contributing to uncontrolled asthma include inappropriate treatment, varying treatment adherence, and comorbidities. A report from the National Review of Asthma Deaths drew attention to avoidable risk factors such as excessive prescribing of reliever medication, the under prescribing of controller medication, and the inappropriate prescribing of long-acting β_2 -agonist (LABA) inhalers (7). Furthermore, notwithstanding the effectiveness of oral corticosteroids (OCS) in controlling acute symptoms and treating exacerbations, their regular use is associated with serious side-effects (8). It is, therefore, important to document the recourse to OCS, to estimate potential overuse (9). Before the arrival of novel biotherapies, it was also important to document actual changes in asthma management. We therefore described asthma care between 2006 and 2016 in France, for the extent of use of controller therapies, healthcare resource utilization, and asthma outcomes rates.

In the absence of asthma diagnoses in claims data (10), and in the context of recent reviews of over- and under-diagnosis of asthma (11) and of adherence data (12), analyses were conducted on two populations: patients with ≥ 1 yearly dispensing of controller therapy (Any Use Population, AUP) and patients with ≥ 4 yearly dispensings of controller therapy (High Use Population, HUP). Almost half of all inhaled corticosteroids (ICS) medication has been shown to be dispensed once yearly, and in addition to asthma, also dispensed for non-asthma conditions such as chronic cough or respiratory tract infections (13) (14). Contrasting these two populations (AUP and HUP) provides an indication of the minimal and maximal extent of the population likely to suffer from persistent asthma. In parallel, attention was given to the use of LABAs, following the conduct of studies focused on the safety of these medications (15). The primary hypothesis was that the quality of asthma care has improved over the last decade. In parallel, we verified the incidence of outcomes over time.

METHODS

Study design

Each year, between 2006 and 2016, repeated transversal analyses were conducted on the EGB (Echantillon Généraliste de Bénéficiaires).

Data source

The EGB is a 1/97th representative random sample of the French national claims database *Système National d'Information Inter-Régimes de l'Assurance Maladie*, which currently covers more than 90% of the French population. EGB records individual anonymous information of primary and secondary care (data from PMSI, the French Diagnosis Related Group-based medical information system) (16, 17). The EGB database contains the following data: (i) General characteristics: gender, year of birth, month and year of death, free-access-to-care status (people socioeconomically disadvantaged are 100% covered), residence area, long-term disease (LTD) status (patients registered for long-term disease benefit from full coverage for all medical expenses, with ICD-10 diagnoses codes, start and end date of LTD) (ii) All non-hospital reimbursed healthcare expenditures with date and code (but not the corresponding medical indication nor result): General Practitioner (GP) visits and medical procedures, lab tests, drugs, and medical devices (iii) Hospital discharge summaries: ICD-10 diagnoses codes (main, related, and associated diagnoses) for all medical, obstetric, and surgery hospitalizations with the date and duration of hospitalization, medical procedures, hospitalization department, and cost coding system.

Regulatory procedures

This observational study was conducted on anonymized data. The National Informatics and Liberty Committee has delivered an overall authorization for using EGB data for research purposes. This study was performed after approval by the French Institute for Health Data (Institut des Données de Santé, approval n° 94, September 9, 2014).

Study population

Analyses were performed on two contrasted populations: a sensitive and a specific population. The sensitive population consisted of patients aged 18-40 years with ≥ 1 dispensing during each calendar year (2006-2016) of an inhaled corticosteroids (ICS; Anatomical Therapeutic Classification (ATC) code: R03BA), or long-acting β_2 agonist (LABA; ATC codes: R03AC12, R03AC13), or fixed dose combination of LABA/ICS (FDC; ATC codes: R03AK06, R03AK07, R03AK08, R03AK10, R03AK11). Patients were excluded if they had a LTD status and/or a hospital admission related to chronic obstructive pulmonary disease (COPD). This population was labelled as “any use population” (AUP).

Four distinct profiles of the AU population were identified: (1) Single ICS without LABA (ICS group); (2) Single LABA without ICS (LABA only group); (3) Single ICS and LABA in separate refills (ICS+LABA group); (4) FDC without dispensing of ICS nor LABA (FDCs group).

The specific population was identified from the therapeutic HEDIS criterion(18) and it consisted of patients aged 18-40 years with ≥ 4 dispensings during each calendar year (2006-2016) of an ICS (ATC

codes: R03BA), or LABA (ATC codes: R03AC12, R03AC13), or FDC (ATC codes: R03AK06, R03AK07, R03AK08, R03AK10, R03AK11). As for the AU population, patients were excluded if they had a LTD status and/or a hospital admission related to chronic obstructive pulmonary disease (COPD). This population was labelled as “high use population” (HUP).

Four distinct profiles of the specific population were identified: (1) ICS group; (2) LABA only group; (3) ICS+LABA group; (4) FDC group.

Study variables

Each year of the study period, patients from both populations (AUP and HUP) were described for the following variables:

- (i) Patients’ characteristics: age, gender, free-access-to-care-status, LTD;
- (ii) Asthma therapy:
 - a. Four distinct profiles: (1) ICS group; (2) LABA only group; (3) ICS+LABA group; (4) FDC group. Each group was described for the percentage of users per year, and the mean yearly number of dispensings was computed;
 - b. Percentages of patients using short-acting β_2 agonists (SABAs), Leukotriene Receptor Antagonist (LTRA) and omalizumab;
- (iii) Healthcare resource utilization (not limited to only asthma related events), including:
 - a. Visits to GPs
 - b. Visits to respiratory physicians or hospital practitioners (available only since 2009)
 - c. Pulmonary function testing (PFT);
- (iv) Outcomes:
 - a. Percentage of patients using OCS (for any condition) and mean annual cumulative dose in prednisone equivalent dose (sum of all the doses in equivalent prednisone of OCS dispensed during the year);
 - b. Emergency room (ER) visits (available only since 2009) and unscheduled medical contacts with GPs for any reason;
 - c. Hospitalization due to asthma (primary diagnosis);
 - d. Death (all causes)

Statistical analysis

Repeated transversal analyses were performed between 2006 and 2016.

Qualitative variables of patient characteristics were described with the sample size within each modality, and relative percentages. Quantitative variables of the healthcare resource utilization were described as a relative percentage, and mean and standard deviation (SD) of patients with ≥ 1 healthcare resource utilization. Changes of asthma controller use were studied in both populations by

213 mean number of refills dispensed per year between 2006 and 2016. Comparisons of patient's
214 characteristics and medical resource utilization in 2006 (or 2009 for visits to respiratory physicians or
215 hospital practitioners) versus 2016 were performed using Chi2 test for qualitative variables, Wilcoxon
216 test for quantitative variables and Fisher's exact test for mortality rates.
217 The statistical analysis was performed using SAS (SAS Institute, North Carolina), version 9.4.

RESULTS

Prevalence of use of asthma controllers in the overall population:

Prevalence of controller use varied little over time in the overall population. In 2006, 4.6% of the national population aged 18 to 40 years met the inclusion criteria for the AU population of controller users. In 2016, 5.2% of the national population fulfilled the AU population criteria, with the highest percentage noted in 2009 at 5.5%. For the HU population of controller users, the prevalence varied between 0.7% of the population in 2006, and 0.8% in 2016.

Characteristics of controller users:

Characteristics of patients included in the AU population (≥ 1 dispensing per year of asthma controller therapy) varied little between 2006 and 2016 (Table 1). Mean age (from 31.2 to 30.8 years; $p=0.15$) and sex-ratio (from 60.7% to 62.1% females; $p=0.07$) remained stable. LTD status and free-access-to-care status also varied little over time. Characteristics of patients included in the HU population were similar to those of the AU population, regarding mean age (from 31.5 to 31.3 years) and free-access-to-care status, but differed for the sex ratio (from 50.8% to 53.1% females). The percentages of patients with long-term disease status were also higher in the HU population (between 7.1% and 9.3%) (Table 2).

TABLE 1

TABLE 2

Relative use of distinct controllers among controller users:

Asthma controller use is represented between 2006 and 2016 in Figure 1. Among all patients of the AU population, use decreased in the LABA only group (from 4.1% to 1.7%; $p<0.01$), in the LABA+ICS group (from 6.2% to 1.6%; $p<0.01$), and in the ICS group (from 44.8% to 40.3%; $p<0.01$). In contrast, use of FDC increased (from 44.8% to 56.4%; $p<0.01$). In the HU population, prevalent use of ICS group was considerably reduced (from 11.2% to 8.7%; $p<0.01$). In the FDC group, prevalent use was higher (69.4% to 84.3%; $p<0.01$). Use decreased significantly in the LABA+ICS group (from 15.9% to 4.8%; $p<0.01$) and LABA use in monotherapy also decreased (from 3.5% to 2.2%; $p<0.01$). SABA use was more frequent in the HU population (72.0% in 2016) than in the AU population (46.2% in 2016). This was also the case for LTRA (10.0% in 2016 in the AU population, and 27.4% in the HU population). Omalizumab was seldom used (less than 0.5% in both populations).

FIGURE 1

Annual controller refills:

Mean numbers of refills dispensed during the study period are presented in Figure 2. In the AU population, annual number of refills was highest in the LABA + ICS group (between 7.9 and 9.0). The FDC and LABA only groups had between 2.3 and 3.0 refills and the ICS group around 1.4 refills per year. In the HU population, in the ICS + LABA group, annual numbers of refills slightly increased (from 15.1 to 16.2). In the FDC group, the mean number of refills varied little (between 7.3 and 7.8). Refill numbers fluctuated slightly in the LABA only group (between 7.9 and 9.3) and in the ICS group (between 5.9 and 7.3).

FIGURE 2

Healthcare resource utilization:

In both populations, the number of visits to GPs decreased with time, as well as the percentage of patients with at least one visit (from 95.9% to 88.6% in the AU population ($p<0.01$), and from 95.7% to 88.3% in the HU population ($p<0.01$)). In contrast, the percentage of patients who visited a respiratory physician or a hospital practitioner increased with time (from 31.6% in 2009 to 37.8% in 2016 for the AU population ($p<0.01$), and from 34.1% in 2009 to 40.5% in 2016 for the HU population ($p<0.01$)), as well as the mean number of visits per year. PFT was always more frequent in the HP population, but it increased with time in both populations, from 9.5% to 12.7% for the AU population ($p<0.01$), and from 18.9% to 27.6% in the HU population ($p<0.01$) (Figure 3 and Figure 4).

FIGURE 3

Outcomes:

In the AU population, the prevalence of use of OCS increased from 42.7% to 50.3% ($p<0.01$), as well as the mean annual cumulative dose, that increased from 674 mg in 2006 to 717 mg in 2016. In the HU population, the prevalence of OCS use remained stable during the 10-year period, but the mean cumulative dose increased from 854 mg to 894 mg (Figure 5). ER visits (all diagnoses combined) increased with time, from 18.0% in 2009 to 24.0% in 2016 for the AU population ($p<0.01$), and from 17.3% in 2009 to 23.7% in 2016 for the HU population ($p<0.01$), while the rates of unscheduled visits decreased in both populations ($p<0.01$) (Figure 3 and Figure 4). Hospitalizations for asthma remained constant in the AU (0.3% in 2016) population but decreased in the HU population (from 1.5% to 0.6%, $p=0.04$) over the ten-year period. They occurred more frequently in the HU population (around 1.0%) than in the AU population (around 0.4%). Mortality rates (all causes) remained stable and low in both populations during this 10-year period (i.e. less than 0.1% in the AU population, and less than 0.2% in the HU population) (Tables 1, 2).

FIGURE 4

292 FIGURE 5

ACCEPTED MANUSCRIPT

DISCUSSION

To support the external validity of the results, two populations were studied in parallel: a more sensitive population, including all patients with ≥ 1 annual controller refill, and a more specific population, including patients with ≥ 4 annual refills of controllers. The algorithm was such that the AU population included the HU population, with more severe asthma or possibly higher adherence, but it also included milder asthma, and non-asthma conditions (11). The prevalence of use of asthma controller therapy slightly varied with time, in the two study populations. In 2016, 5.2% of the national population aged 18-40 years met the inclusion criteria for the AU population, while the prevalence was 0.8% for the HU population. Among both populations, between 2006 and 2016, prevalent use decreased significantly in the LABA only group, in the LABA+ICS group, and in the ICS group, whereas it increased in the FDC group. SABA use was more frequent in the HU than in the AU population (72.0% vs. 46.2% in 2016). In the AU population, annual number of refills was higher in the FDC group (2.3 to 3.0 refills) than in the ICS group (1.3 to 1.4 refills per year). The percentage of patients who visited a respiratory physician or a hospital practitioner, and the incidence of PFT increased with time, while the number of visits to GPs decreased in both populations. In parallel to changes in asthma care, there was an increased incidence of adverse outcomes, with increased use of OCS from 42.7% to 50.3% in the AU population. Concomitantly, ER visits (all diagnoses combined) increased significantly over time. Hospitalizations rates for asthma remained low in both populations over the ten-year period, but hospital admissions occurred more frequently in the HU population than in the AU population.

Sex ratio differed between the two populations: there were 60% of women in the AU population, compared to 50% in the HU population. The difference was also illustrated by the percentages of patients with LTD status, a marker of disease severity, more common in the HU population (9% versus 2% in the AU population). The HU population did likely include patients with high adherence, and hence better outcomes, but overall adherence in asthma is known to be poor (12), for all levels of severity, and the contribution by good adherers to the overall outcomes was likely to be limited. The differences between these two populations underline the impact of the criteria applied for persistent asthma selection. Indeed, in claims data, identification of asthma has to be made in the absence of clinical diagnosis, and contrasted selections (AUP vs. HUP) are of interest to distinguish care and outcomes in milder and more severe conditions.

Few studies have reported trends of use of asthma controller therapy in the general population. Nevertheless, our results could be compared to those obtained by Ekerljung et al. who reported an increased use of asthma medication in the Gothenburg population aged 21-46, from 7.8% in 1992 to 12% in 2010, mainly due to an increased use of ICS in monotherapy from 1.5% to 7.7% (19).

Davidson (20) showed in an asthma cohort aged 18-44 that the overall annual prevalence of ICS use remained constant in 1997-2000 (approximately 64% of all controller use), but gradually increased to 77% in 2006, due to an increased use of FDCs. An increase in FDC use continues to be observed, certainly in France, where FDCs tend to be introduced at lower levels of severity (21). Our data also showed that patients taking LABA+ICS and LABA decreased with time, in agreement with recommendations (22), to start controller therapy with ICS only (22). Our data suggesting that a majority of persistent asthma patients are treated early with FDCs could however be supported by the results of recent trials showing a better effectiveness of FDCs over ICS (23) (24) (25) (26) (27), possibly due to improved adherence with FDCs (28). Moreover, the introduction of FDCs in patients with milder asthma could possibly be accepted as a reference strategy, preferentially for products that include formoterol (29) (30) (31).

Current asthma treatment guidelines (32) also recommend using quick-relief medications on an as-needed basis rather than as a regularly scheduled medication. Despite these recommendations and well-documented adverse effects of excessive SABA use, our data are in line with other studies suggesting an overuse of SABA (5) (33). Indeed, in the HU population, around 70% of patients had at least one refill of SABAs, with a mean number of six refills per year.

In addition to asthma therapy, the study shows a large increase of the number of patients visiting a respiratory physician or a hospital practitioner, up to 40.5%, and 37.8% in 2016 in the HU and the AU populations, respectively. Whilst, the specialty of hospital practitioner is not recorded, and therefore not all visits can be attributed to asthma management, this change clearly reflects a change in asthma care, away from primary care and towards secondary care. In line with increased secondary care visits, a concurrent increase in PFT during the 10-year period was also observed.

Regarding markers of asthma outcomes, hospital admissions were more frequent in the HU population (around 1%), in agreement with previous studies conducted in France (34). Unscheduled visits to GPs decreased in both populations while ER visits markedly increased with time. This was also the case for OCS dispensings in the AU population. For these potential markers of asthma outcomes (emergency room visits, unscheduled visits and OCS), information on diagnoses or reasons of visits/prescriptions were not available. It affects the interpretation of the results, but in this young population (less than 40 years) asthma is likely explaining the major part of medical resource utilization, as already described in previous studies (35) (36).

This study is important as it explored patterns of use of therapy in datasets comprising large numbers of patients, and which exhaustively record all dispensed therapy. A limitation of claims data is however the absence of disease diagnostic codes, so that persistent asthma patients were identified

using 2 algorithms (age criteria and controller dispensings, either ≥ 1 or ≥ 4 yearly). Based on these algorithms, asthma patients untreated with any controller were not included in the study. Furthermore, to avoid the risk of including COPD and other respiratory diseases, the selection was made according to age. This excluded part of severe asthma patients (i.e. patients aged more than 40 years).

The database did also not contain the indication of therapy. Indeed, ICS could be prescribed for cough or bronchitis, and OCS may be prescribed and dispensed for several conditions. Furthermore, asthma outcomes were mostly identified with markers (OCS, ER visits, unscheduled medical contacts), except for hospital admission, that was recorded with asthma as a primary diagnosis.

Inappropriate use of asthma therapy use was frequently reported, and is considered to be one of the main causes of adverse asthma outcomes, resulting in increased number of ER visits. A concomitant decrease in the number of visits to GPs have also been observed, suggesting that in acute situations, patients preferentially visit secondary care physicians instead of GPs. In parallel, increasing number of patients received FDCs and OCS. Conversely, increased number of visits to respiratory physicians or to hospital practitioners, as well as pulmonary function testing was observed, suggesting an improvement in asthma care. LABA only group and LABA+ICS group decreased with time, in agreement with recommendations (32). Indeed, the safety of LABAs remains controversial in asthma, which led regulators to contraindicate LABAs as a single agent in asthma treatment (37).

In conclusion, prevalent use of asthma controller therapy varied little between 2006 and 2016, whether patients were identified from at least one, or four, refills per year. FDCs tended to replace ICS, particularly in more severe asthma. In parallel, prevalent use of SABAs and OCS use increased with time. An increased number of visits to respiratory physician or to hospital practitioner, as well as more frequent PFT were observed. Concomitantly, ER visits increased significantly over time, and hospitalizations rates for asthma remained low in both populations over the ten-year period.

In summary, changes in asthma care included increased involvement of specialized or secondary care at the expense of primary care. In parallel, despite stable figures for hospital admissions and mortality, overall use of OCS and incidence of ER visits have increased over the last ten years, suggesting that patient care needs further improvement.

Bibliography

1. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach [Available from: http://www.who.int/gard/publications/GARD_Manual/en/.]
2. Guideline N. Asthma: diagnosis, monitoring and chronic asthma management 2017 [Available from: <https://www.nice.org.uk/guidance/ng80>]
3. Reddy AP, Gupta MR. Management of asthma: the current US and European guidelines. *Adv Exp Med Biol.* 2014;795:81-103.
4. Ebmeier S, Thayabaran D, Braithwaite I, Benamara C, Weatherall M, Beasley R. Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012). *Lancet.* 2017;390(10098):935-45.
5. Belhassen M, Nibber A, Van Ganse E, Ryan D, Langlois C, Appiagyei F, et al. Inappropriate asthma therapy-a tale of two countries: a parallel population-based cohort study. *NPJ Prim Care Respir Med.* 2016;26:16076.
6. Laforest L, Pacheco Y, Bousquet J, Kocevar VS, Yin D, Van Ganse E. How appropriate is asthma therapy in general practice? *Fundam Clin Pharmacol.* 2005;19(1):107-15.
7. Deaths NRoA. Why asthma still kills. 2014.
8. Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ primary care respiratory medicine.* 2015;25:15026.
9. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol.* 2013;9(1):30.
10. Moulis G, Lapeyre-Mestre M, Palmaro A, Pugnet G, Montastruc JL, Sailer L. French health insurance databases: What interest for medical research? *Rev Med Interne.* 2015;36(6):411-7.
11. Aaron SD, Boulet LP, Reddel HK, Gershon A. Under-diagnosis and Over-diagnosis of Asthma. *Am J Respir Crit Care Med.* 2018.
12. Laforest L, Belhassen M, Devouassoux G, Didier A, Ginoux M, Van Ganse E. Long-Term Inhaled Corticosteroid Adherence in Asthma Patients with Short-Term Adherence. *The journal of allergy and clinical immunology In practice.* 2016;4(5):890-9.e2.
13. Poulos LM, Ampon RD, Marks GB, Reddel HK. Inappropriate prescribing of inhaled corticosteroids: are they being prescribed for respiratory tract infections? A retrospective cohort study. *Prim Care Respir J.* 2013;22(2):201-8.
14. Deprez Ph-H CF, Clech S, Vallier N, Germanaud J, Weill A, Cornille JL, Fender P, Allemand H et le groupe Médipath. La population traitée par médicaments de la classe des antiasthmatiques en France métropolitaine : données du régime général de l'assurance maladie, 2000 [The population treated with antiasthmatic drugs in metropolitan France: data from the general health insurance scheme, 2000]. *Revue Médicale de l'Assurance Maladie.* 2004;35 n° 1(janvier-mars 2004).
15. Van Ganse E, Texier N, Dima AL, Laforest L, Ferrer M, Hernandez G, et al. Assessment of the safety of long-acting beta2-agonists in routine asthma care: the ASTRO-LAB protocol. *NPJ Prim Care Respir Med.* 2015;25:15040.
16. Martin-Latry K, Begaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can! *Pharmacoepidemiol Drug Saf.* 2010;19(3):256-65.

17. Tuppin P, Rudant J, Constantinou P, Gastaldi-Menager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: From the system national d'information interregimes de l'Assurance Maladie (SNIIRAM) to the system national des donnees de sante (SNDS) in France. *Rev Epidemiol Sante Publique*. 2017;65 Suppl 4:S149-S67.
18. National Committee for Quality Assurance. HEDIS & performance measurement. 2018 [Available from: <http://www.ncqa.org/HEDISQualityMeasurement.aspx>].
19. Ekerljung L, Bjerg A, Bossios A, Axelsson M, Toren K, Wennergren G, et al. Five-fold increase in use of inhaled corticosteroids over 18 years in the general adult population in west Sweden. *Respir Med*. 2014;108(5):685-93.
20. Davidsen JR. Drug utilization and asthma control among young Danish adults with asthma. Analyses of trends and determinants. *Dan Med J*. 2012;59(8):B4501.
21. Raherison C, Bourdin A, Bonniaud P, Deslee G, Garcia G, Leroyer C, et al. Updated guidelines (2015) for management and monitoring of adult and adolescent asthmatic patients (from 12 years and older) of the Societe de Pneumologie de Langue Francaise (SPLF) (Full length text). *Rev Mal Respir*. 2016;33(4):279-325.
22. 2018 GINA Report, Global Strategy for Asthma Management and Prevention [Available from: <https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>].
23. Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, et al. Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone. *N Engl J Med*. 2016;374(19):1822-30.
24. Peters SP, Bleecker ER, Canonica GW, Park YB, Ramirez R, Hollis S, et al. Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone. *N Engl J Med*. 2016;375(9):850-60.
25. Suissa S, Israel E, Donohue J, Evans S, Kemp J. Food and Drug Administration-mandated Trials of Long-Acting beta-Agonist Safety in Asthma. Bang for the Buck? *American journal of respiratory and critical care medicine*. 2018;197(8):987-90.
26. Stempel DA, Szeffler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, et al. Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma. *N Engl J Med*. 2016;375(9):840-9.
27. Busse WW, Bateman ED, Caplan AL, Kelly HW, O'Byrne PM, Rabe KF, et al. Combined Analysis of Asthma Safety Trials of Long-Acting beta2-Agonists. *N Engl J Med*. 2018;378(26):2497-505.
28. Laforest L, Belhassen M, Devouassoux G, Didier A, Ginoux M, Van Ganse E. Long-Term Inhaled Corticosteroid Adherence in Asthma Patients with Short-Term Adherence. *J Allergy Clin Immunol Pract*. 2016;4(5):890-9 e2.
29. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. *N Engl J Med*. 2018;378(20):1877-87.
30. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *N Engl J Med*. 2018;378(20):1865-76.
31. Lazarus SC. On-Demand versus Maintenance Inhaled Treatment in Mild Asthma. *N Engl J Med*. 2018;378(20):1940-2.
32. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J*. 2015;46(3):622-39.

- 486 33. Shireman TI, Heaton PC, Gay WE, Cluxton RJ, Moomaw CJ. Relationship between asthma
487 drug therapy patterns and healthcare utilization. *Ann Pharmacother*. 2002;36(4):557-64.
- 488 34. Belhassen M, Langlois C, Laforest L, Dima AL, Ginoux M, Sadatsafavi M, et al. Level of
489 Asthma Controller Therapy Before Admission to the Hospital. *The journal of allergy and clinical*
490 *immunology In practice*. 2016;4(5):877-83.
- 491 35. Jacob C, Bechtel B, Engel S, Kardos P, Linder R, Braun S, et al. Healthcare costs and
492 resource utilization of asthma in Germany: a claims data analysis. *Eur J Health Econ*.
493 2016;17(2):195-201.
- 494 36. Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, et al. The epidemiology,
495 healthcare and societal burden and costs of asthma in the UK and its member nations: analyses
496 of standalone and linked national databases. *BMC Med*. 2016;14(1):113.
- 497 37. Chowdhury BA, Dal Pan G. The FDA and safe use of long-acting beta-agonists in the
498 treatment of asthma. *N Engl J Med*. 2010;362(13):1169-71.

499 **Table 1: Characteristics of asthma controller therapy users with ≥ 1 dispensing per year (AU population)**

	2006 N =6,151	2007 N =6,913	2008 N =6,901	2009 N =7,885	2010 N =7,605	2011 N =8,231	2012 N =8,519	2013 N =8,222	2014 N =8,054	2015 N =8,338	2016 N =9,202	<i>p</i> ***
Mean age (+/- SD)	31.2 (6.1)	31.2 (6.2)	31.2 (6.2)	30.9 (6.5)	30.7 (6.5)	30.9 (6.3)	30.9 (6.3)	30.9 (6.3)	30.9 (6.3)	30.8 (6.3)	30.8 (6.3)	0.15
Women, n (%)	3,732 (60.7)	4,190 (60.6)	4,213 (61.0)	4,797 (60.8)	4,687 (61.6)	5,082 (61.7)	5,162 (60.6)	5,027 (61.1)	4,914 (61.0)	5,132 (61.5)	5,715 (62.1)	0.07
Free access care status, n (%)	906 (14.7)	1,019 (14.7)	973 (14.1)	1,029 (13.1)	1,114 (14.6)	1,193 (14.5)	1,235 (14.5)	1,215 (14.8)	1,267 (15.7)	1,325 (15.9)	1,453 (15.8)	0.07
LTD for asthma, n (%)	140 (2.3)	135 (2.0)	156 (2.3)	155 (2.0)	149 (2.0)	177 (2.2)	153 (1.8)	162 (2.0)	175 (2.2)	163 (2.0)	182 (2.0)	0.21
Death (all causes), n (%)	5 (0.08%)	6 (0.09%)	4 (0.06%)	6 (0.08%)	6 (0.08%)	10 (0.12%)	7 (0.08%)	4 (0.05%)	6 (0.07%)	6 (0.07%)	5 (0.05%)	0.53
Visits to GP												
Number of patients, n (%)	5,901 (95.9)	6,630 (95.9)	6,632 (96.1)	7,578 (96.1)	7,202 (94.7)	7,574 (92.0)	7,576 (88.9)	7,269 (88.4)	7,076 (87.9)	7,318 (87.8)	8,152 (88.6)	<0.01
Mean number of visit per patient (+/-SD)	6.8 (6.6)	6.8 (6.3)	6.6 (6.0)	6.5 (5.6)	6.4 (5.7)	6.3 (5.3)	6.2 (5.4)	6.2 (5.4)	6.3 (5.4)	6.0 (5.2)	6.1 (5.2)	
Visits to a respiratory physician or a hospital practitioner*												
Number of patients, n (%)	-	-	-	2,489 (31.6)	2,502 (32.9)	2,747 (33.4)	2,822 (33.1)	2,966 (36.1)	2,986 (37.1)	3,089 (37.0)	3,477 (37.8)	<0.01
Mean number of visit per patient (+/-SD)	-	-	-	2.7 (3.4)	2.8 (3.1)	2.8 (3.5)	3.0 (3.5)	3.1 (3.3)	3.2 (4.8)	3.5 (5.6)	3.8 (4.4)	
PFT, n (%)	584 (9.5)	604 (8.7)	678 (9.8)	844 (10.7)	894 (11.8)	906 (11.0)	1,002 (11.8)	971 (11.8)	1,023 (12.7)	1,016 (12.2)	1,167 (12.7)	<0.01
Unscheduled visits to GPs* n (%)	619 (10.1%)	700 (10.1%)	642 (9.3%)	766 (9.7%)	668 (8.8%)	753 (9.1%)	704 (8.3%)	696 (8.5%)	718 (8.9%)	761 (9.1%)	499 (5.4%)	<0.01
ER visits * n (%)	-	-	-	1,418 (18.0)	1,468 (19.3)	1,718 (20.9)	1,744 (20.5)	1,841 (22.4)	1,871 (23.2)	1,960 (23.5)	2,204 (24.0)	<0.01
Hospitalizations for asthma, n (%)	29 (0.5)	24 (0.3)	20 (0.3)	22 (0.3)	24 (0.3)	20 (0.2)	26 (0.3)	30 (0.4)	30 (0.4)	30 (0.4)	30 (0.3)	0.15

Dispensing of OCS												
≥1 dispensing, n (%)	2,629 (42.7)	3,186 (46.1)	3,162 (45.8)	3,657 (46.4)	3,548 (46.7)	3,973 (48.3)	4,212 (49.4)	4,015 (48.8)	4,006 (49.7)	4,089 (49.0)	4,631 (50.3)	<0.01
Mean number of units** (+/-SD)	1.9 (2.7)	1.9 (2.6)	1.9 (2.3)	1.9 (2.6)	1.9 (2.6)	1.9 (2.6)	1.9 (2.2)	2.0 (2.7)	1.9 (2.6)	1.9 (2.9)	1.9 (2.5)	
Mean annual cumulative dose of OCS in prednisone equivalent dose (+/-SD)	674.3 (812.1)	670.5 (639.2)	676.7 (606.7)	682.9 (737.7)	671.3 (636.9)	691.7 (684.1)	693.3 (558.7)	711.8 (664.4)	696.7 (726.0)	703.9 (628.6)	717.4 (626.2)	
Dispensing of SABAs												
≥1 dispensing, n (%)	2,687 (43.7)	2,833 (41.0)	2,683 (38.9)	3,267 (41.4)	3,182 (41.8)	3,484 (42.3)	3,780 (44.4)	3,671 (44.6)	3,812 (47.3)	3,846 (46.1)	4,252 (46.2)	<0.01
Mean number of refill**, (+/-SD)	3.1 (4.8)	3.1 (3.9)	3.2 (4.1)	2.9 (3.8)	2.9 (3.8)	2.9 (3.6)	2.9 (3.7)	2.9 (3.6)	3.0 (3.8)	2.9 (3.6)	2.9 (3.5)	
Dispensing of LTRA												
≥1 dispensing, n (%)	583 (9.5)	668 (9.7)	667 (9.7)	763 (9.7)	839 (11.0)	937 (11.4)	975 (11.4)	934 (11.4)	935 (11.6)	890 (10.7)	920 (10.0)	
Mean number of refill**, (+/-SD)	3.6 (3.8)	3.6 (3.7)	3.9 (3.9)	3.8 (3.9)	3.9 (3.9)	3.9 (3.9)	3.9 (3.9)	4.1 (4.0)	4.1 (4.1)	4.4 (4.1)	4.3 (4.1)	0.03
Dispensing of omalizumab												
≥1 dispensing, n (%)	2 (0.0)	5 (0.1)	6 (0.1)	6 (0.1)	0 (0.0)	3 (0.0)	3 (0.0)	3 (0.0)	7 (0.1)	9 (0.1)	8 (0.1)	0.33

*All medical specialties

**In patients with at least one dispensing of the drug

*** p value when comparing 2006/2009 versus 2016 results

LTD: long-term disease status; GP: general practitioner; PFT: pulmonary function testing; ER: emergency room; OCS: oral corticosteroids; SABAs: short acting beta agonists; LTRA: Leukotriene Receptor Antagonist

507 **Table 2: Characteristics of asthma controller therapy users with ≥ 4 dispensings per year (HU population)**

	2006 N =964	2007 N =1,040	2008 N =1,078	2009 N =1,095	2010 N =1,105	2011 N =1,222	2012 N =1,244	2013 N =1,227	2014 N =1,309	2015 N =1,271	2016 N =1,441	<i>p</i> ***
Mean age (+/- SD)	31.5 (5.9)	31.4 (6.1)	31.6 (6.0)	31.9 (6.2)	31.6 (6.3)	31.6 (6.1)	31.2 (6.2)	31.3 (6.2)	31.2 (6.3)	31.1 (6.1)	31.3 (6.1)	0.05
Women, n (%)	490 (50.8%)	548 (52.7%)	575 (53.3%)	583 (53.2%)	590 (53.4%)	657 (53.8%)	654 (52.6%)	635 (51.8%)	685 (52.3%)	676 (53.2%)	765 (53.1%)	0.28
Free access care status, n (%)	134 (13.9%)	162 (15.6%)	161 (14.9%)	162 (14.8%)	165 (14.9%)	157 (12.8%)	174 (14.0%)	184 (15.0%)	206 (15.7%)	183 (14.4%)	229 (15.9%)	0.18
LTD for asthma, n (%)	90 (9.3%)	88 (8.5%)	101 (9.4%)	96 (8.8%)	81 (7.3%)	100 (8.2%)	93 (7.5%)	98 (8.0%)	97 (7.4%)	85 (6.7%)	102 (7.1%)	0.05
Death (all causes), n (%)	0 (0.00%)	2 (0.19%)	0 (0.00%)	1 (0.09%)	0 (0.00%)	1 (0.08%)	1 (0.08%)	1 (0.08%)	0 (0.00%)	1 (0.08%)	2 (0.14%)	0.52
Visits to GP												
Number of patients, n (%)	923 (95.7%)	1,007 (96.8%)	1,030 (95.5%)	1,054 (96.3%)	1,049 (94.9%)	1,112 (91.0%)	1,106 (88.9%)	1,104 (90.0%)	1,143 (87.3%)	1,104 (86.9%)	1,273 (88.3%)	<0.01
Mean number of visit per patient (+/-SD)	7.1 (8.0)	7.0 (5.8)	7.2 (7.7)	7.2 (6.8)	6.9 (6.1)	6.8 (5.9)	6.7 (6.1)	6.6 (6.2)	6.6 (5.9)	6.4 (5.7)	6.3 (5.2)	
Visits to a respiratory physician or a hospital practitioner*												
Number of patients, n (%)	-	-	-	373 (34.1%)	383 (34.7%)	398 (32.6%)	454 (36.5%)	450 (36.7%)	516 (39.4%)	468 (36.8%)	584 (40.5%)	<0.01
Mean number of visit per patient (+/-SD)	-	-	-	3.0 (3.1)	2.9 (3.3)	3.1 (3.5)	3.3 (4.4)	3.1 (3.6)	3.3 (3.4)	3.3 (3.6)	3.9 (4.8)	
PFT, n (%)	182 (18.9%)	190 (18.3%)	225 (20.9%)	263 (24.0%)	273 (24.7%)	278 (22.7%)	313 (25.2%)	318 (25.9%)	354 (27.0%)	311 (24.5%)	398 (27.6%)	<0.01
Unscheduled visits to GPs* n (%)	88 (9.1%)	82 (7.9%)	104 (9.6%)	93 (8.5%)	74 (6.7%)	106 (8.7%)	81 (6.5%)	79 (6.4%)	110 (8.4%)	95 (7.5%)	72 (5.0%)	<0.01
ER visits * n (%)	-	-	-	189 (17.3%)	198 (17.9%)	238 (19.5%)	266 (21.4%)	275 (22.4%)	288 (22.0%)	271 (21.3%)	341 (23.7%)	<0.01
Hospitalizations for asthma, n (%)	14 (1.5%)	10 (1.0%)	9 (0.8%)	12 (1.1%)	9 (0.8%)	8 (0.7%)	12 (1.0%)	13 (1.1%)	13 (1.0%)	15 (1.2%)	9 (0.6%)	0.04
Dispensing of OCS												
≥ 1 dispensing, n (%)	449 (46.6%)	476 (45.8%)	496 (46.0%)	476 (43.5%)	498 (45.1%)	563 (46.1%)	563 (45.3%)	543 (44.3%)	610 (46.6%)	558 (43.9%)	676 (46.9%)	0.87

Mean number of units** (+/- SD)	2.3 (3.9)	2.2 (2.5)	2.4 (3.2)	2.5 (3.1)	2.3 (2.8)	2.6 (4.2)	2.5 (3.7)	2.6 (4.2)	2.6 (4.9)	2.7 (4.9)	2.7 (4.7)	
Mean annual cumulative dose of OCS in prednisone equivalent dose (+/-SD)	854.0 (1,374.2)	815.4 (875.7)	847.4 (868.5)	915.2 (971.4)	827.5 (804.2)	895.1 (940.3)	857.2 (876.8)	889.4 (1,078.0)	923.9 (1,467.3)	898.3 (852.0)	893.5 (922.3)	
Dispensing of SABAs												
≥1 dispensing, n (%)	663 (68.8%)	689 (66.3%)	716 (66.4%)	750 (68.5%)	741 (67.1%)	811 (66.4%)	866 (69.6%)	833 (67.9%)	918 (70.1%)	919 (72.3%)	1,037 (72.0%)	0.09
Mean number of refill**, (+/- SD)	6.1 (7.5)	6.0 (5.7)	6.1 (5.7)	5.9 (5.6)	5.8 (5.9)	5.7 (5.6)	5.6 (5.5)	5.6 (5.6)	5.8 (6.0)	5.6 (5.0)	5.6 (5.1)	
Dispensing of LTRA												
≥1 dispensing, n (%)	225 (23.3)	277 (26.6)	268 (24.9)	286 (26.1)	317 (28.7)	354 (29.0)	373 (30.0)	360 (29.3)	376 (28.7)	356 (28.0)	395 (27.4)	
Mean number of refill**, (+/- SD)	6.1 (4.3)	5.7 (4.1)	6.3 (4.3)	6.6 (4.3)	6.6 (4.1)	6.4 (4.2)	6.6 (4.2)	6.8 (4.2)	6.9 (4.4)	7.4 (4.1)	7.0 (4.2)	0.03
Dispensing of omalizumab												
≥1 dispensing, n (%)	2 (0.2)	4 (0.4)	5 (0.5)	5 (0.5)	0 (0.0)	3 (0.2)	2 (0.2)	2 (0.2)	4 (0.3)	4 (0.3)	5 (0.3)	0.71

*All medical specialties

**In patients with at least one dispensing of the drug

***p value when comparing 2006/2009 versus 2016 results

LTD: long-term disease status; GP: general practitioner; PFT: pulmonary function testing; ER: emergency room; OCS: oral corticosteroids; SABAs: short acting beta agonists; LTRA: Leukotriene Receptor Antagonist

Figure 1: Prevalence of controllers use

Figure 2: Mean number of refills during the 2006-2016 study period

Figure 3: Health care resources utilisation and markers of asthma outcomes in the AU population

Figure 4: Health care resources utilisation and markers of asthma outcomes in the HU population

Figure 5: Evolution of oral corticosteroids use during the 2006-2016 study period

Authors' contributions:

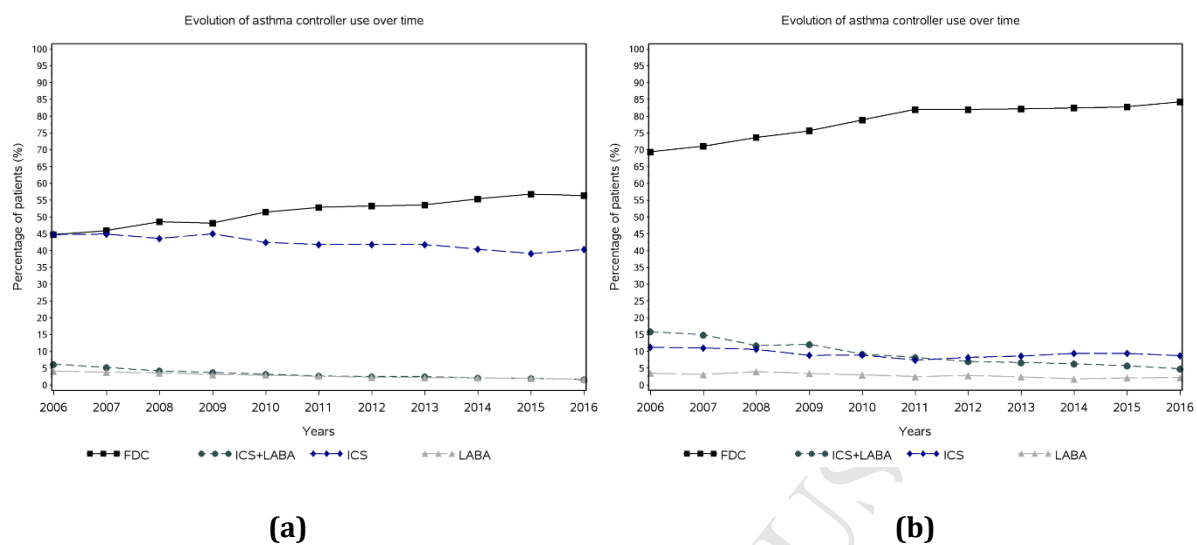
All authors critically reviewed the manuscript.

MB and EVG provided supervision, conceived and designed the study, interpreted the data, and drafted the manuscript. MN did the statistical analysis. MG, AN and GD contributed to study design and interpretation of data. MB is the guarantor of the study.

Funding source:

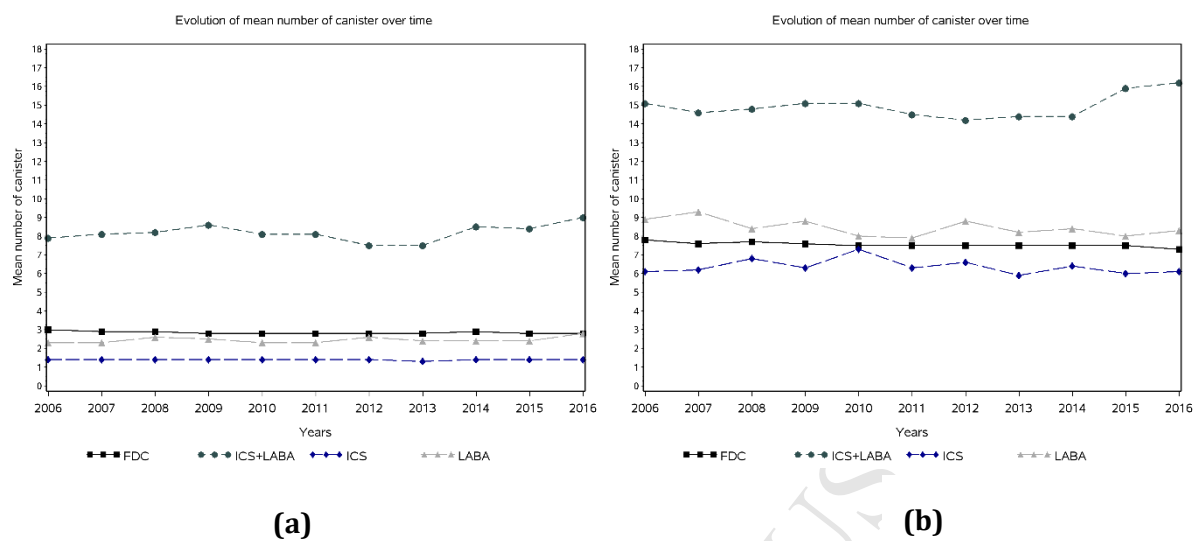
No funding source.

MB had full access to all the data in the study, and had the final responsibility for the decision to submit for publication.

Figure 1: Prevalence of controllers use: (a) AU population; (b) HU population

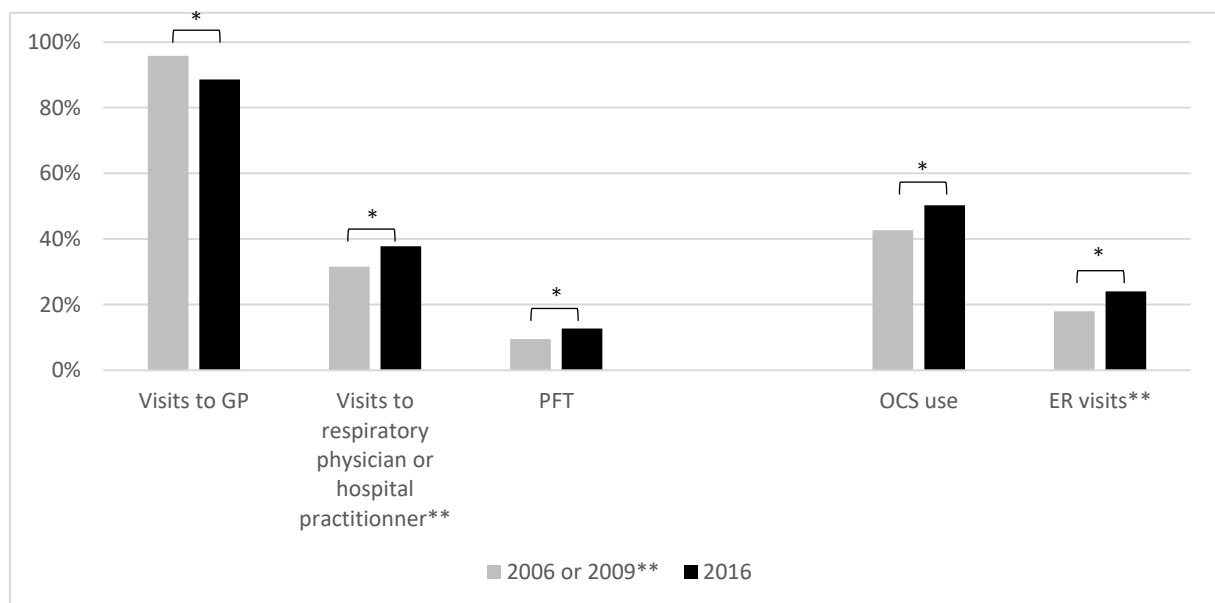
LABA: long-acting β_2 -agonist; ICS: inhaled corticosteroids; FDC: fixed dose combination of LABA/ICS

Figure 2: Mean number of refills during the 2006-2016 study period: (a) AU population; (b) HU population



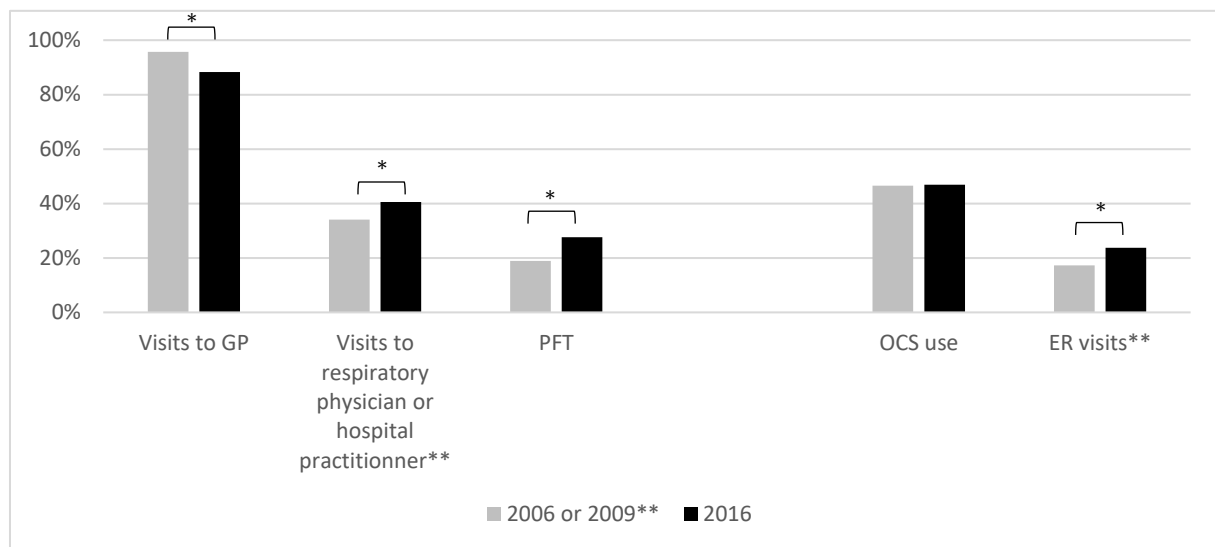
LABA: long-acting β_2 -agonist; ICS: inhaled corticosteroids; FDC: fixed dose combination of LABA/ICS

Figure 3: Health care resources utilisation and markers of asthma outcomes in the AU population



* P value < 0.05 when comparing 2006/2009 vs 2016

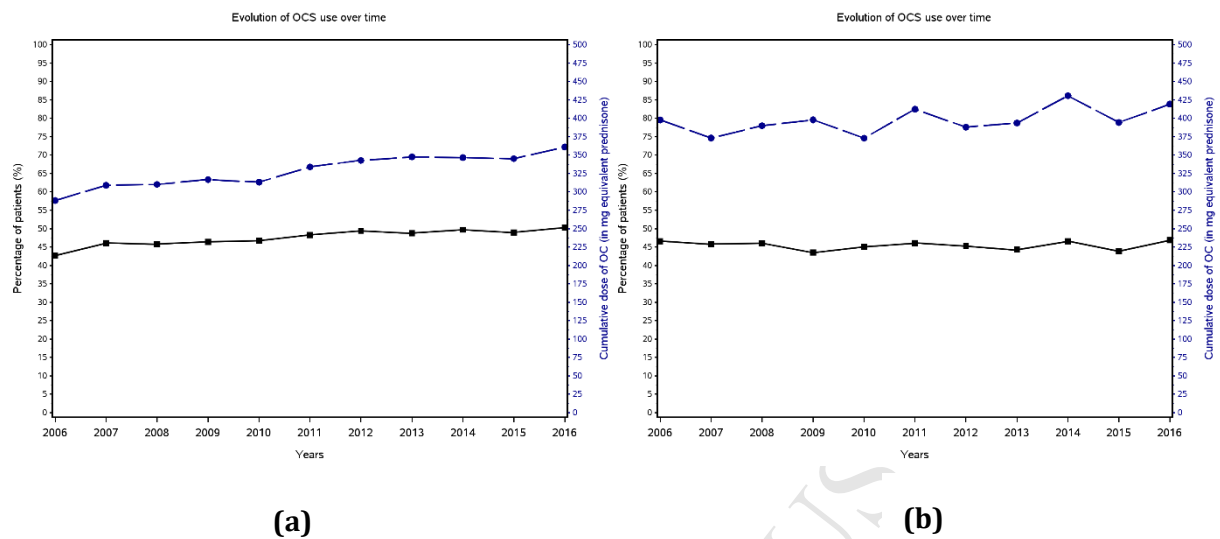
GP: general practitioner; PFT: pulmonary function testing; OCS: oral corticosteroids; ER: emergency room

Figure 4: Health care resources utilisation and markers of asthma outcomes in the HU population

* P value < 0.05 when comparing 2006/2009 vs 2016

GP: general practitioner; PFT: pulmonary function testing; OCS: oral corticosteroids; ER: emergency room

Figure 5: Evolution of oral corticosteroids use during the 2006-2016 study period: (a) AU population; (b) HU population



OCS: oral corticosteroids