Asthma therapeutic management : a pharmacoepidemiological approach

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Prise en charge thérapeutique de l'asthme : une approche pharmaco-épidémiologique

Asthma therapeutic management: a pharmacoepidemiological approach

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RESUME

L'asthme est un problème de Santé publique au niveau mondial. Il touche environ 10% des enfants et des adultes en France, avec des conséquences socio-économiques importantes. L'asthme est une maladie respiratoire chronique obstructive complexe, caractérisée par une hétérogénéité phénotypique et une expression clinique variable au cours du temps. Les essais contrôlés randomisés restent la référence pour évaluer l'efficacité et la sécurité des médicaments. Néanmoins, les études pharmaco-épidémiologiques, nécessaires pour compléter les résultats des essais contrôlés randomisés, restent encore limitées dans l'asthme. Cette thèse en pharmaco-épidémiologie, s'appuyant sur deux cohortes françaises complémentaires, avait pour objectif d'améliorer la compréhension de la qualité de la prise en charge thérapeutique de l'asthme en population. Les objectifs spécifiques étaient d'étudier: 1) les bénéfices à long terme des corticoïdes inhalés dans l'asthme, 2) le ratio « traitements de fond/traitements des pathologies respiratoires obstructives », défini à partir des données médico-administratives, et ses fluctuations au cours du temps chez les sujets âgés, et 3) la polymédication dans l'asthme du sujet âgé.

L'efficacité à court terme des corticoïdes inhalés a largement été démontrée mais leurs bénéfices à long terme ont rarement été étudiés. Nous avons estimé les effets à long terme des corticoïdes inhalés sur 245 adultes asthmatiques participant à l'étude EGEA. L'application d'une méthode par score de propension pour prendre en compte le biais d'indication n'a pas permis de mettre en évidence un bénéfice à long terme des corticoïdes inhalés utilisés au long cours sur la santé respiratoire. Un bénéfice potentiel de l'exposition aux corticoïdes inhalés au long cours a toutefois été observé sur l'évolution de la fonction respiratoire. Plusieurs indicateurs de qualité de prise en charge de l'asthme, basés principalement sur des bases de données administratives américaines, ont été proposés dans l'enfance et à l'âge adulte. Cependant, la pertinence de tels indicateurs n'a pas été spécifiquement étudiée dans des populations plus âgées et leurs fluctuations au cours du temps n'ont jamais été caractérisées. Notre étude menée auprès de 4328 femmes asthmatiques âgées de l'étude Asthma-E3N a montré que le ratio « traitements de fond/traitements des pathologies respiratoires obstructives », défini à partir des bases de données médico-administratives, est un indicateur pertinent pour identifier les sujets âgés à risque de mauvais contrôle de la maladie. De plus, l'étude de la variation à long terme du ratio a permis d'identifier des groupes de femmes asthmatiques présentant un risque élevé d'asthme non contrôlé à terme. La population âgée souffre fréquemment de multimorbidité, conduisant à la polymédication et potentiellement à une réponse altérée au traitement. L'impact des comorbidités et de leurs traitements reste inconnu. Nous avons appliqué une méthode intégrative à partir des bases de données de remboursements des médicaments chez les femmes asthmatiques de l'étude Asthma-E3N. Le « Pharmacome » a confirmé la polymédication dans cette population et a mis en évidence les liens entre les médicaments. En appliquant une méthode de classification sur les classes thérapeutiques des médicaments utilisés, nous avons identifié trois profils de femmes asthmatiques présentant un niveau de risque différent de mauvais contrôle de la maladie.

En conclusion, les données médico-administratives représentent une source pertinente pour identifier les patients à haut risque de mauvais pronostic d'asthme au niveau populationnel. Notre travail en pharmaco-épidémiologie apporte une nouvelle approche sur l'évaluation de la prise en charge thérapeutique de l'asthme et sur l'interrelation entre les médicaments de l'asthme et les autres médicaments, proxies de comorbidités. Nos résultats sont d'une importance particulière, en raison du fardeau mondial de l'asthme. Ils s'inscrivent dans la politique de santé des gouvernements qui doivent faire face à l'accroissement exponentiel de la multimorbidité et au vieillissement des populations.

Mots-clés : pharmaco-épidémiologie ; asthme ; médicaments ; qualité de prise en charge.

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ABSTRACT

Asthma is a worldwide non-communicable disease affecting around 10% of children and adults in France, with substantial socio-economic impacts. This is a complex chronic respiratory disease characterized by phenotypic heterogeneity and fluctuations of clinical expression over time. Randomized controlled trials (RCT) remain the gold standard to assess medication efficacy and safety. Nevertheless, pharmacoepidemiological studies have a helpful design to complement RCT findings, but are still limited in asthma. This thesis in pharmacoepidemiology, relying on two complementary French cohorts, aimed to add information on the assessment of the quality of asthma therapeutic management in real life. Specific aims were to investigate: i) the long-term benefits of inhaled corticosteroids in asthma, ii) the controller-to-total asthma medication ratio and its fluctuations over time in the elderly, and iii) the polymedication in elderly asthma.

The short-term efficacy of inhaled corticosteroids on asthma has been largely established, but their long-term benefits have rarely been assessed. We estimated the long-term effects of inhaled corticosteroids on 245 adults with persistent asthma who participated to the EGEA study. Applying a propensity score method to take into account the indication bias did not offer evidence of a statistical significant long-term benefit of ICS used regularly or continuously over twelve years on respiratory health. However, a trend for benefits of long-term ICS exposure was observed on lung function evolution. Asthma therapeutic management in the elderly relies on studies performed in younger populations, postulating that its efficacy is similar in this specific population. Some quality of care markers, mainly based on US drug administrative databases, have been proposed in childhood and adulthood with asthma. However, the relevance of such asthma medication ratios has been poorly addressed in older populations, and its fluctuations over time have never been characterized. Our study, conducted among 4,328 elderly women with ever asthma from the Asthma-E3N study and using drug administrative databases, showed that the controller-to-total asthma medication ratio is also relevant in the elderly and identified specific patterns of fluctuations of the ratio significantly associated with the subsequent risk for poor asthma-related outcomes. The elderly population frequently suffers from multimorbidity, leading to polymedication and potential altered response to treatment. To which extent asthma-related comorbidities and their treatments impact on asthma phenotypes and medications remains unknown. Therefore, we applied an integrative method on a drug administrative database to characterize the medication network in elderly women with asthma from the Asthma-E3N study. The medication network ("Pharmacome") in elderly asthma confirmed the complexity of therapeutic management in this population and highlighted links between medications. Applying a clustering method on drug use among participants with asthma, we identified three clusters of individuals characterized by their profiles of treatment use, which showed different risk levels for subsequent poor asthma characteristics (uncontrolled asthma, asthma attacks/exacerbations, impaired health-related quality of life).

In conclusion, our findings are both of public health and clinical interests. Claims data are relevant to identify patients at high risk for poor asthma prognosis at the population level. Our work in pharmacoepidemiology, relying on health administrative databases, provides new insights into the assessment of asthma therapeutic management and the inter-relationship between asthma medications and medications for comorbid conditions. Our results are of particular importance, first given the global burden of asthma, which needs ongoing monitoring aimed at identifying patients at risk for poor health-related outcomes, and secondly given the population ageing, which needs better insights in the multimorbidity.

Keywords: pharmacoepidemiology; asthma; treatments; quality of care.

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PREAMBLE

My interest for research began early during my pharmaceutical studies and motivated me to embark on a PhD. As pharmacist student and, now, pharmacist, my decisions are driven by evidence-based medicine, and mainly on randomized controlled trials, the gold standard to assess medication efficacy and safety. As I progressed in my professional career, I experienced discrepancies between randomized controlled trials and real life, suggesting a lack of knowledge about medication use at the population level, which piqued my interest in the pharmacoepidemiology field. It was during my residency in clinical pharmacy in pneumology that I discovered the complexity of asthma, a burden disease that is not fully elucidated. I therefore started a PhD to study the pharmacoepidemiology of asthma in the team of "Environmental Epidemiology applied to Reproduction and Respiratory Health" at the Institute for Advanced Biosciences (Grenoble, France). I have conducted my PhD work while having a university hospital assistant position at Grenoble Alpes University and Hospital, therefore being teacher and clinical pharmacist at the same time. This thesis on pharmacoepidemiology of asthma is obviously part of the willingness to combine a research activity with hospital and academic activities.

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ABBREVIATIONS

ABPA	Allergic bronchopulmonary aspergillosis
ACOS	Asthma-COPD overlap syndrome
ACT	Asthma control test
AQLQ	Asthma quality of life questionnaire
ATC	Anatomical Therapeutic Chemical
Bac.	Baccalaureate
BMI	Body mass index
BMRC	British Medical Research Council
CCHS	Copenhagen City Heart Study
COPD	Chronic obstructive pulmonary disease
E3N	Etude Epidémiologique auprès de femmes de la MGEN
ECRHS	European Community Respiratory Health Survey
ECSC	European Coal and Steel Community
EGEA	Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy
ETS	Environmental tobacco smoke
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GERD	Gastro-oesophageal reflux disease
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HDAC2	Histone deacetylase-2
HRQL	Health-related quality of life

ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin
IPTW	Inverse probability treatment weighting
IUATLD	International Union against Tuberculosis and Lung Disease
LABA	Long-acting beta$_2$-agonists
LCA	Latent class analysis
LTRA	Leukotriene receptor antagonists
m	Mean
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
MGEN	Mutuelle Générale de l'Education Nationale
OR	Odd ratio
OSA	Obstructive sleep apnea
OCS	Oral corticosteroids
RCT	Randomized clinical trials
SABA	Short-acting beta$_2$-agonists
SD	Standard deviation

TABLE OF CONTENTS

CHAPTER I

GENERAL INTRODUCTION

This state of the art consists of two parts; the first part is an overview of asthma, introducing the complexity of the disease, its pathophysiological features and aetiologies, before focusing on asthma therapeutic management; the second part relates to the pharmacoepidemiological approach in asthma and raises the major challenges in this research field.

I. ASTHMA: BURDEN OF A COMPLEX DISEASE

Asthma is a worldwide non-communicable disease resulting of complex interactions between genes, environment and behaviours. Asthma therapeutic management follows international guidelines, but is hampered by the important endo-phenotypic heterogeneity of the disease.

A. Clinical features of asthma

Asthma is a chronic airway disease, whose definition remains controversial, some even query the possibility of merging many heterogeneous phenotypes within this entity (1). Asthma is characterized by variable respiratory symptoms, including recurrent episodes of shortness of breath with wheezing in chest, coughing and chest tightness, due to variable airway obstruction, reversible spontaneously or under treatment effect, and bronchial hyperresponsiveness (2). The diagnosis of asthma may be difficult due to the absence of gold standard. It relies on a detailed medical history, a physical examination and pulmonary function testing (2). The first step is based on patient's interview and medical examination, and consists on the assessment of respiratory signs and symptoms, including features, frequency, intensity, age at onset, triggers, and circumstances and time of occurrence. For patients presumed to have asthma, pulmonary function testing is performed, using most often spirometry to measure forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), but also to calculate instant flows at different levels of the vital capacity. Airflow obstruction is defined by an FEV_1/FVC ratio <2 standard deviation (SD) from the normal value (varying with age). Significant reversibility of airway obstruction is defined by an improvement in FEV_1 >12% of the baseline value after short-acting $beta_2$-agonists (SABA). Additional tests may be needed to confirm the diagnosis of asthma, such as

bronchoprovocation test to assess airway responsiveness. In some situations, the diagnosis of asthma may be hampered by differential diagnosis, including chronic obstructive pulmonary disease, which can coexist in old patients, defined by fixed airway obstruction (3, 4). Asthma severity, which represents the intrinsic activity of the disease, is assessed at diagnosis but may vary over time from intermittent to mild, moderate or severe persistent asthma, according to symptoms, their day- and night-time frequency, and lung function. Persistent asthma is defined as daytime symptoms occurring more than two days or less per week and potentially interfering with normal activities, nighttime symptoms occurring more than two times per month, and normal (mild persistent asthma) or abnormal (moderate and severe persistent asthma) lung function tests. Asthma management, previously relied on this classification of asthma severity, is currently focused on asthma control.

One of the most important features of asthma is that it cannot be cured but its clinical expression can be controlled with appropriate therapies. The control of asthma is the main challenge of disease management (2). Asthma symptom control is evaluated by the disease activity, estimated by day- and night-time symptoms, hospitalisations, reliever treatment use, the impact on occupational and exercise, the occurrence of exacerbations, and the level of bronchial obstruction, over a short period of time, usually within two to four weeks (2, 5). The assessment of asthma symptom control can be easily done in clinical practice by standardized questionnaires, such as the asthma control test (ACT) (5).

Asthma is a disease with varying clinical manifestations over time. Often appearing in childhood, asthma can remain stable throughout life, disappear for several years, recur, and worsen at any age. Temporal variability of asthma acute manifestations (e.g., asthma attacks) relies on a complex system integrating interactions between immunological and inflammatory mechanisms, but also potentially environmental stimuli. Asthma acute manifestations can be classified as asthma attack, asthma exacerbation and acute exacerbation, according to their

duration and intensity. Asthma attack is defined by paroxisms of respiratory symptoms (cough, dyspnea, wheeze) over a short period of time (i.e., less than a day). Symptoms lasting more than 48 hours without returning at baseline define asthma exacerbation, mainly due to viral infections or allergic reactions. Asthma exacerbation severity can be estimated by the combination of corticosteroid therapy required duration, the level of peak expiratory flow decrease and emergency healthcare use (i.e., urgent medical consultation, emergency department admission, and hospitalisation). Severe forms of acute asthma are either acute exacerbation of asthma, associated with respiratory, hemodynamic or neurologic failures, leading to acute severe asthma corresponding to status asthmaticus, or sudden asthma attack characterized by an acute and severe onset. Beyond the acute manifestations, asthma has chronic consequences related to airway remodelling and chronic inflammation (6). Patients with asthma have a more rapid lung function decline than healthy people, which can be accelerated by persistent asthma and severe asthma exacerbations (7).

B. Epidemiology and burden of asthma

1. Definition of asthma in epidemiology

Asthma is commonly defined by questionnaire in epidemiological studies. Standardized questionnaires have been developed in Europe in the 1960s through the British Medical Research Council (BMRC) and the European Coal and Steel Community (ECSC) (8). The American Thoracic Society Epidemiology Standardization Project recommended an adaptation to the BMRC questionnaire by the National Heart and Lung Institute to define asthma in 1978 (9). The International Union against Tuberculosis and Lung Disease (IUATLD) developed a new questionnaire in the 1980s with more information on asthma and mainly focused on respiratory symptoms in the past 12 months (10). The European

Community Respiratory Health Survey (ECRHS) questionnaire, widely used in recent studies, is largely based on the IUATLD questionnaire.

Ever asthma is commonly defined by a positive answer to the question “Have you ever had asthma attack?” or “Have you ever had asthma?”, such as in the Asthma-E3N (Etude Epidémiologique auprès de femmes de la Mutelle Générale de l’Education Nationale, MGEN) study (9). A recent study suggested that the repeated answer to the question “Have you ever had asthma attack?” over time improves the assessment of ever asthma, limiting potential misdiagnosis (11). Specific combinations of questions on respiratory symptoms are reliable predictors of current asthma in epidemiological studies (12, 13). An asthma symptom score based at least on five symptoms over the last 12 months has been proposed to define a continuous scale of asthma (13, 14). Such a score improves statistical power when analysing risk factors and give additional information to the dichotomous definitions allowing to better assess the disease heterogeneity (13, 14). In some studies, the protocol includes objective tests of lung function and airway responsiveness, like the EGEA (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy) study (15).

2. Prevalence and incidence of asthma

The World Health Organization estimates that more than 300 million people of all age are affected with asthma in the world. The burden of asthma is growing with an additional 100 million people expected to develop asthma worldwide by 2025 (16). Asthma prevalence varies greatly between countries (from 0.2% in China to 21% in Australia in 2002-2003), affects mostly industrialized countries, and is associated with the adoption of urban lifestyle in developing countries (17, 18). Overall, the prevalence of ever asthma has increased over the past 30 years to reach approximately 4.3% (95%CI, 4.2;4.4) in adults (16, 17, 19) (Figure 1). In Europe, asthma prevalence has doubled in the 1960-1990 period, affecting 8.2% of

adults and 9.4% of children, before reaching a plateau since the mid-1990s (20, 21). In France, current asthma affects around 10% of children and 7% of adults, with more boys being affected in childhood and a reversal of the sex ratio at puberty (17, 22).

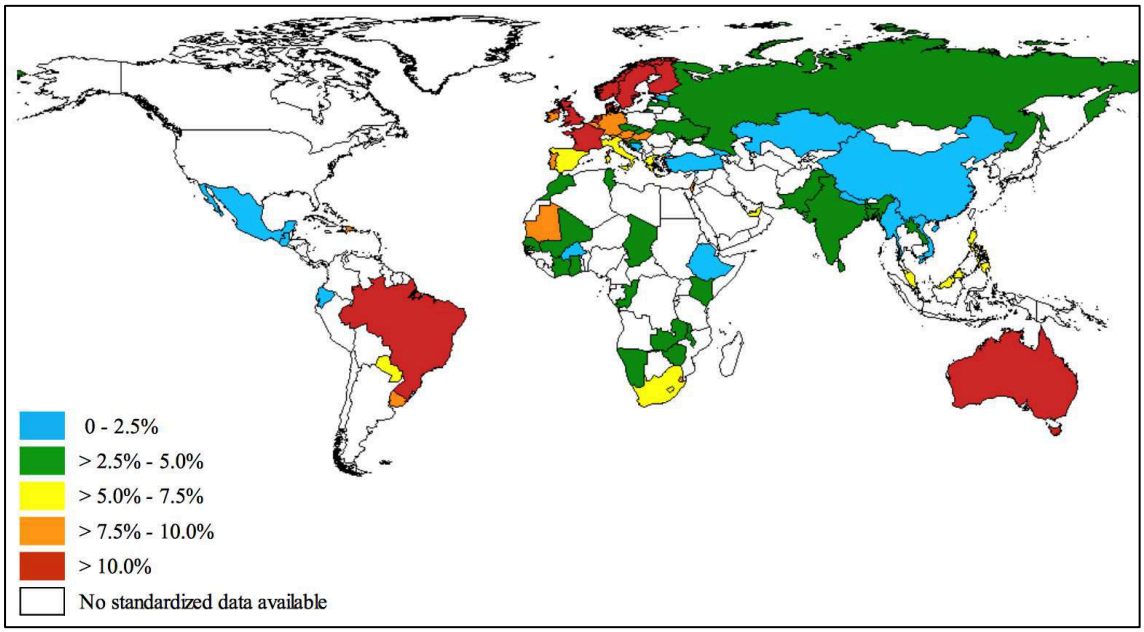


Figure 1. Worldwide prevalence of clinical asthma according to the World Health Survey. (17)

The incidence rate of asthma in children from 5 to 9 years was estimated at 27.9 cases per 1000 person-years in Ontario in 2012 (23). A significant decrease of incidence rate is observed with age, to reach 5.9 and 4.4 per 1000 person-years in the early 2000s, among women and men of the general population, respectively (24). However, a higher incidence was reported by several studies among those older than 50 years, probably due to misclassification with chronic obstructive pulmonary disease (COPD) (23, 24).

3. Asthma burden

Disability among subjects with asthma is common and costly. Asthma was ranked as the 15th leading cause of disability in terms of years of life lost in good health among 301 acute and chronic diseases and injuries in 2013 (25). Although the number of deaths from asthma has declined in recent years, asthma remains the 32nd cause of years of life lost over

240 causes of death in 2010 (26). Asthma-related mortality is estimated at more than 180,000 deaths per year in the world (20). In France, asthma leads to more than 50,000 hospitalizations and 1,000 deaths each year (22). Nearly two-thirds of deaths from asthma are preventable by improving asthma management and patients' therapeutic education (27).

The socio-economic consequences of asthma are substantial, both in terms of direct (medications, doctor visits, hospitalization) and indirect costs (sick leave, absenteeism, premature death). In Europe, the total cost of asthma was estimated at € 33 billions in 2011, including € 14 billions of indirect costs (28). Around € 1.5 billion per year were allocated to asthma management in France in 2001 (20, 29, 30).

The major public health impact relates to difficult-to-control asthma. Asthma can often be treated effectively with medications, but a large part of the population with asthma remains inadequately controlled, due to lack of regular treatment, poor compliance, irregular medical follow-up, or drug resistance (31). Uncontrolled asthma accounts for one third of patients with asthma in Europe, with a significant geographic variability (20% to 67% depending on the country) (2, 31). In France, one third of patients with asthma may have uncontrolled asthma (31). The socio-economic impact of poor controlled asthma is considerable. It leads to a significant decrease in quality of life, including an increased risk of anxiety or depressive episodes, and is a large part of the direct and indirect costs associated with asthma, in terms of absenteeism, treatment or hospitalization (30, 32). As compared to controlled asthma, poor controlled asthma leads to additional costs from € 516 to € 1,812/patient/year, in partially controlled and uncontrolled asthma, respectively (30). In conclusion, asthma is a common chronic disease associated with significant morbimortality, highlighting its importance in terms of public health.

4. Aetiologies of asthma

There is no single known cause of asthma, but there are several factors that may contribute to the condition. Asthma results from the interplay between genetic, environmental and behavioural factors (2). Asthma has a strong family resemblance and the role of genetic factors in asthma development is well established both in children and adults (33). In the past decade, genome-wide association studies offered new opportunities to decipher the role of genetic polymorphisms in such complex diseases (34). A large number of genes have been identified in asthma, but a small proportion of these genes have been replicated, and genes identified so far explained only a small fraction of the disease heritability (the "missing heritability") (35). Part of the missing heritability could be explained by the shared environment and the phenotypic heterogeneity, some genetic factors might be specifically associated with specific phenotypes. Gene-environment interactions are involved in asthma incidence and severity (e.g., interaction with active and passive smoking, occupational exposures) and research in asthma genetics currently focuses on more complex gene-gene and gene-environment interactions (36-38). Besides the role of genetics, there is growing scientific evidence that supports the role of epigenetic mechanisms in the development of asthma and allergic diseases (39, 40). Epigenetic mechanisms could explain environmental effects, parental and multi-generational origin, plasticity during the development or the pharmacological effects of some treatments. Epigenetic modifications are related to asthma expression in the long term (incidence, response to treatment), occur particularly in utero and in childhood but also during the life course, and are reversible over time (41-43).

The asthma prevalence increase over the last decades cannot be due to genetic modifications, and points out the role of environmental and behavioural factors, in particular those that changed within the same time window. Many risk factors or triggers can be implied both in disease onset, its evolution and its expression over time. Risk factors for asthma

incidence or asthma triggers include personal factors (i.e., sex, gender, allergy, obesity, stress, strong emotion), behavioural factors (i.e., dietary habits, smoking [in utero, passive and active], physical activity, some medications such as aspirin or other non-steroidal anti-inflammatory drugs), occupational factors (e.g., isocyanates, latex, aldehydes, metals, flour…), indoor (i.e., molds, dust, mites, cockroaches, pet dander, cleaners, phenols, phtalates), and outdoor environment factors (i.e., pollens, respiratory infections [especially viral infections], atmospheric pollution in short- and long-term, weather patterns/changes, cold and dry air) (2, 44, 45). Beside the risk factors, research also focused on protective factors, especially at the early stages of life when the immune and pulmonary system matures, within the framework of the hygiene hypothesis. Growing in a diverse microbial environment, such as in farms, collective childcare or with domestic animals, is associated with a lower risk of allergic diseases, including asthma (especially allergic asthma phenotypes) (46). This hypothesis has evolved and relates to the microbiome hypothesis. Recent investigations suggest the microbiome as a key player in the pathophysiology and regulation of this disease (47, 48). Both innate and adaptive immune functions may alter airway as well as gut microbiomes, leading to disease onset or poor prognosis. A new therapeutic approach based on microbiota may be outlined for asthma treatments and prevention.

C. Heterogeneity of asthma

The pathophysiological mechanisms of asthma are complex and remain still partially known. Asthma involves many mediators that interplay between each other (Figure 2). The pathophysiology of asthma is based on the combination of i) a chronic inflammation associated with airway hyperresponsiveness and characterized by cellular infiltration of the airway walls (eosinophils, neutrophils, monocytes and T lymphocytes); ii) a bronchial smooth muscle contraction; iii) mucus hypersecretion; and iv) lesions of the bronchial epithelium.

The mast cell plays a key role in the pathophysiology of asthma since it is the target of immunological reactions, and it releases mediators causing asthma attack. The importance of these pathophysiological mechanisms evolves over time, characterizing the chronicity of the disease.

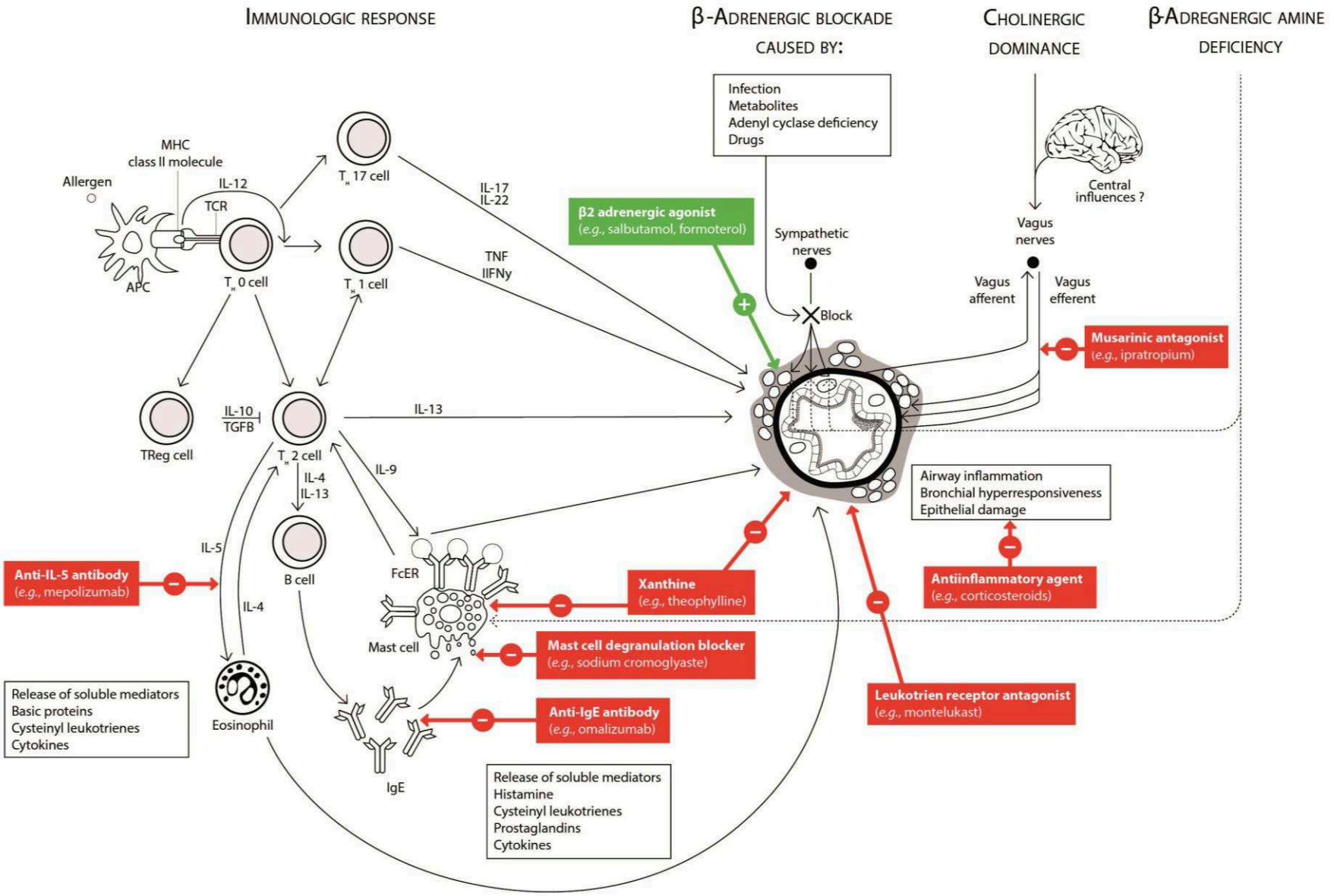


Figure 2. Pathophysiology and pharmacological targets of asthma. Adapted from (49, 50)

1. Asthma endo-phenotypes

The concept of asthma has largely evolved over time (51). From a single disease, asthma has become a heterogeneous disease covering multiple phenotypes, defined as the "observable properties of an organism produced by the interactions of the genotype and the environment" (52). It even suggested that asthma is a syndrome including several different diseases rather than a single disease characterized by a constellation of related, but distinct, disease phenotypes (53, 54). Many asthma phenotypes have been identified from demographic, clinical (e.g., severity of the disease, evolution over time) and pathophysiological (e.g., allergy, age at asthma onset, obesity) features, the most common including being allergic/non-allergic asthma, childhood onset/adult-onset asthma, asthma with fixed airflow limitation, and asthma with obesity (Figure 3) (2, 51). Each phenotype may differ from its aetiology, natural history, clinical manifestations, and underlying mechanisms (53). Interestingly, asthma phenotypes related to response to treatment have also been proposed (1, 55, 56). Steroid resistant asthma, usually found in patients with severe asthma, is an asthma phenotype whose aetiology remains unclear (1).

Recently, some molecular pathways related to clinical manifestations of the disease have been identified, leading to consider a new concept of asthma classification, asthma "endotypes" (e.g., allergic bronchopulmonary mycosis, aspirin-exacerbated respiratory disease, severe late-onset hypereosinophilic asthma). Two main "endotypes" related to inflammatory type have been characterized, type 2 High and type 2 Low, and are particularly of interest for targeted biologic therapy (Figure 3) (51). Nevertheless, no strong evidence has been found between specific pathological features and clinical patterns or treatment responses.

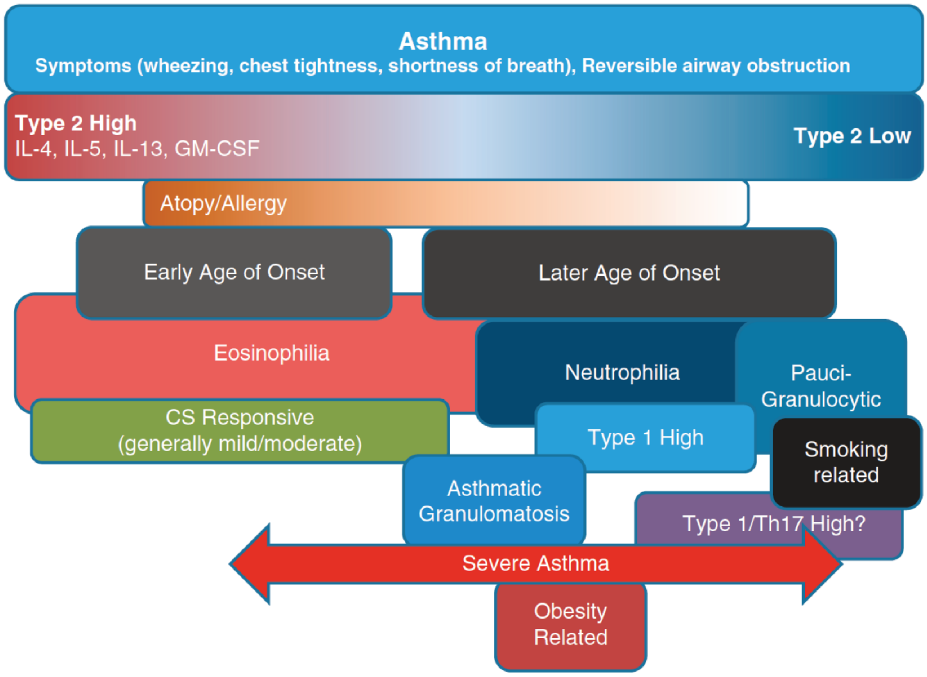


Figure 3. Current asthma phenotypes classification. (51)

2. Asthma in the elderly

Asthma in the elderly is a particular phenotype, of growing interest in the context of population ageing (57). The prevalence of asthma in older adults, defined as aged at least 64 years old (58), is similar to the prevalence in younger adults and children (5-10%) (59). However, asthma in the elderly is characterized by a higher rate of mortality (i.e., two-thirds of deaths attributed to asthma) (60), healthcare expenditures (i.e., healthcare use and medications) (61, 62), worsened by common comorbid conditions in this age group, leading to an additional cost of 13% or more (58, 63). Predominant and more severe in women (60, 64), asthma in the elderly is characterized by at least two main phenotypes: late-onset asthma, with a disease onset after 40 years old, and long-standing asthma, with persistent childhood (or early adulthood) onset asthma (57, 59, 65). These features highlight the need to improve asthma management in the elderly.

Underdiagnosis and misdiagnosis are important issues in the elderly. Asthma might be diagnosed in only half of the elderly with asthma (66). The reduced perception of symptoms, the particular/non specific clinical features of the disease leading potentially to attribute them to other causes, but also the underuse of objective assessment are widely found in this age group (58, 67). An integrative approach consisting of symptom assessment, spirometry, comorbidity assessment should be considered both for asthma diagnosis and management in the elderly.

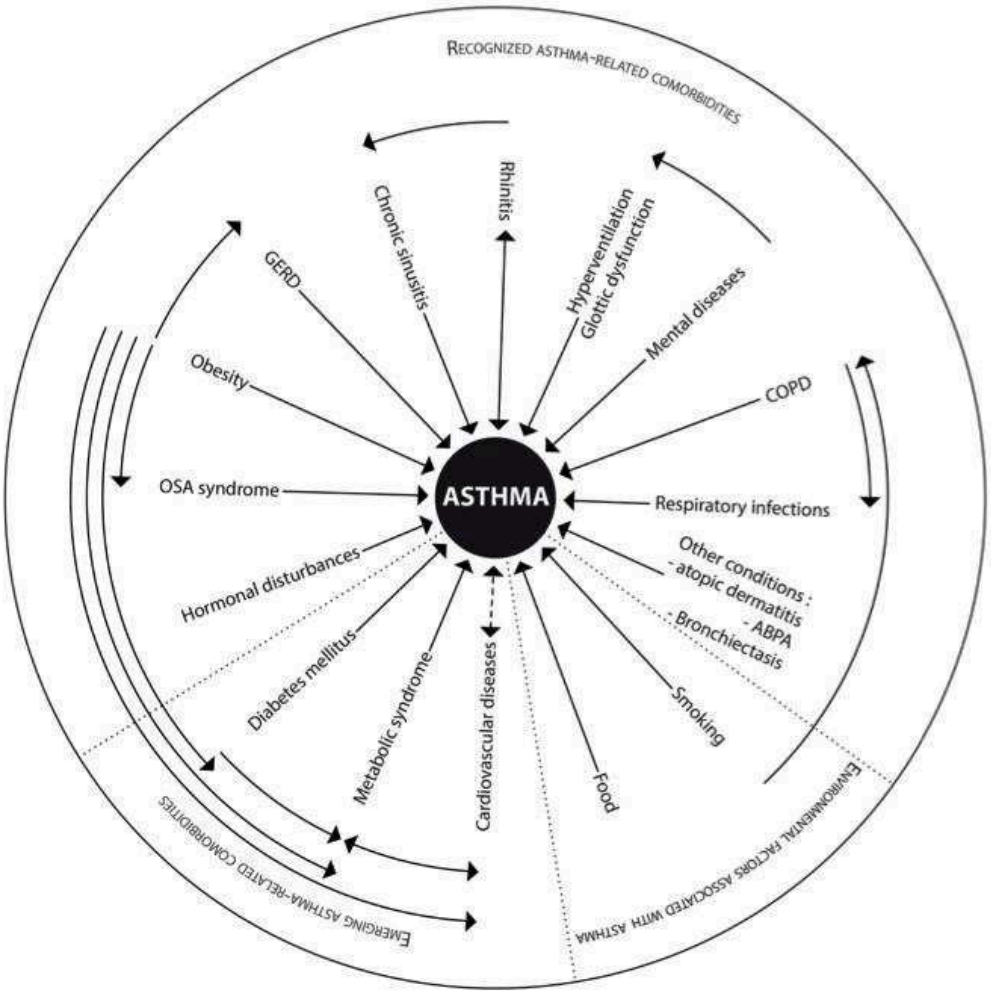
Asthma therapeutic management is a major challenge in the elderly. Asthma in the elderly is widely undertreated (66). Its therapeutic management is not considered as a specific condition in international guidelines but extrapolated from findings of many randomized controlled trials (RCT) performed in younger populations (2, 58, 68). Asthma therapeutic management in the elderly is hampered by multiple factors including pharmacokinetic and pharmacodynamic changes, a potential lower response to treatment, comorbid conditions common in advanced age, and polypharmacotherapy (i.e., leading to drug-drug interactions and potential adverse drug reactions) (3, 59, 64, 65, 67). Current asthma medications have poorly been tested among old people with asthma in real life.

3. Comorbidities in asthma

The multimorbidity, characterized by two or more chronic diseases, is an issue of growing importance, as it represents over 50% of adults aged over 65 years old, and leads to a five-time increase in healthcare expenditures compared to non-multimorbidity (69, 70). A multidimensional approach consisting in considering comorbidities is required in asthma management and asthma research, to gain insight in the complex reality of asthma, particularly in the context of population ageing.

Asthma is commonly associated with several comorbid conditions, particularly in difficult-to-treat or severe asthma, and in the elderly, the latter increasing not only the risk of comorbidity but also the risk of multimorbidity (2, 71, 72). The prevalence of comorbid conditions is higher in asthma than in other chronic diseases (73, 74). A recent study estimated that old people with asthma had eight comorbidities on average versus 3.4 for those in younger adults (75). Various comorbid conditions or factors are involved as risk factors, modifying factors or consequences of asthma (Figure 4). Some asthma-related comorbidities and factors have been identified in adults with asthma and may affect the diagnosis of the disease, the disease control/severity, the lung function, the health-related quality of life, and the asthma medication response (73, 76, 77). A recent study estimated an average overall excess cost at $ 1058/person-year among patients with asthma suffering from comorbidities, of which 65.1% was attributable to comorbidities (78). The most common asthma-related comorbidities and factors include rhinosinusitis, nasal polyps, gastro-oesophageal reflux disease, obesity, obstructive sleep apnea (OSA), lower airway diseases, psychological disturbances (e.g., anxiety, depression, panic disorders), hormonal disturbances, chronic infections, especially respiratory virus infections, food allergy, and anaphylaxis (73). Lower airway diseases are of particular interest, as common comorbid conditions with asthma, potentially leading to misdiagnosis and undertreatment. Chronic obstructive pulmonary disease is an important condition leading to misdiagnosis of asthma particularly in the elderly because of similar clinical expression features (2, 3, 58, 79). The coexistence of asthma and COPD (mainly due to smoking exposure) has been defined as asthma-COPD overlap syndrome (ACOS), and its management has been recently characterized in national and international guidelines (2, 3, 79). Emerging comorbid conditions have been recently proposed, such as diabetes mellitus, metabolic syndrome, and cardiovascular diseases (i.e., hypertension, congestive heart disease) (80). Nevertheless, the link between asthma and

cardiovascular diseases is controversial, cardiovascular complications being attributed to asthma treatment (74).



ABPA, Allergic bronchopulmonary aspergillosis; GERD, Gastro-oesophageal reflux disease; OSA, Obstructive sleep apnea.

Figure 4. Comorbidities associated with asthma. Adapted from (73, 74, 80)

As previously described, comorbid conditions may have different way to influence asthma severity (i.e., through their role either in similar pathophysiological pathways, or in disease evolution towards a different asthma phenotype, or in modifying the disease characteristics, or in a specific phenotype) (2, 73). To which extent each comorbidity or cluster of diseases, as suggested recently by Kankaaranta et al (80), and their treatments are

involved in asthma-related outcomes and how it affects long-term asthma-related outcomes and therapies remain to elucidate.

The identification and assessment of the impact of comorbidities on asthma have to be an integral part of the core management of asthma, particularly in difficult-to-treat asthma (73, 74). The impact of comorbidity-related treatments on asthma characteristics and medications is sparsely known (74, 81). Research in asthma-related comorbidities and their treatments is needed to help asthma management in clinical practice.

D. Asthma therapeutic management

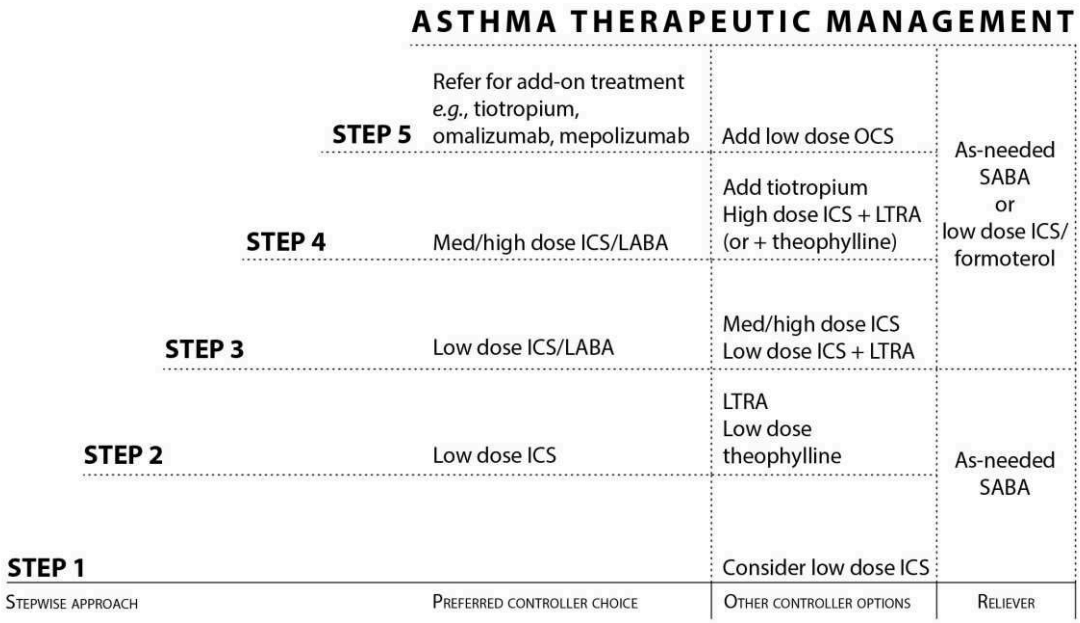
Asthma management is based, in addition to the control of environmental factors, on reliever therapy for symptoms, attacks or exacerbations, but also on maintenance therapy to prevent the occurrence and limit symptom intensity. Asthma treatments still cannot cure asthma but aim to control the disease (elimination or reduction of symptoms, prevention of exacerbations and airway obstruction, quality of life improvement), by reducing airway inflammation and preventing airway obstruction.

Asthma treatment evolved considerably over the last twenty years from theophylline, the first bronchodilator used in asthma but currently seldom used because of its weak efficacy and common side effects, to asthma medication associations and, more recently, to the emergence of targeted biological therapies (Figure 2). Asthma maintenance therapy has been the subject of numerous national and international guidelines (2). Asthma therapeutic management is currently based on three targets involved in the pathophysiological process of asthma: inflammation, bronchoconstriction, and cellular reactions in asthma allergic phenotypes. Asthma treatments should be initiated as soon as possible after the diagnosis. Response to treatment has to be reviewed from one to three months after treatment initiation, and every three to twelve months thereafter if no acute manifestation.

Asthma therapeutic management is adjusted up or down in a stepwise approach to achieve the control of the disease and minimize future risk of exacerbations, fixed airflow limitation and medication side effects (Figure 5) (2). In the stepwise approach, one should always first consider the common problems frequently encountered, including incorrect inhaler technique, poor adherence and avoidance of environmental exposure, before modifying the level of therapy.

Inhaled corticosteroids (ICS) are the cornerstone of asthma maintenance therapy and are introduced as regular controller medications in low, medium or high doses according to the clinical expression of the disease. Other pharmacological classes can be combined with corticosteroid therapy according to the control of the disease, i.e., LABA, cromones, leukotriene receptor antagonists (LTRA), or xanthines (Figure 5). Recently, anticholinergics have been introduced in international guidelines as add-on therapy for patients aged more than 12 years with a history of exacerbations (82). Asthma requiring a high level of maintenance therapy (i.e., steps 4 and 5 according to the Global Initiative for Asthma [GINA] classification) or systemic corticosteroids at least half of the previous year to control the disease or remaining uncontrolled despite these therapies is defined as severe asthma (83).

Reliever asthma treatments include SABA, possibly associated with short-acting muscarinic antagonists, systemic corticosteroids and rarely short-acting theophylline. Formoterol (LABA) is as effective as SABA as reliever medication in adults and children, but the frequent use of formoterol without ICS is strongly not recommended because of the risk of exacerbations (2).



ICS, Inhaled corticosteroids; LABA, Long-acting beta$_2$-agonists; LTRA, Leukotriene receptor antagonists; OCS, Oral corticosteroids; SABA, Short-acting beta$_2$-agonists.

Figure 5. Asthma therapeutic management in adulthood and children older than 5 years old. Adapted from (2)

Inhaled administration should remain the preferred route of administration in asthma maintenance therapy, in particular to limit the occurrence of systemic adverse effects. Several medical devices are available for inhaled administration: puffers “spray” with or without spacer device, dry powder inhalers, and nebulisers. Patient education plays a key role in asthma management to ensure optimal adherence and appropriate use of associated medical devices, especially in specific populations such as the elderly (84).

Asthma therapeutic management remains a hot topic at the international level. The use and place of LABA is controversial in asthma (85). Initially approved for asthma maintenance therapy in the 1990s, increased risk of severe exacerbations and mortality among patients treated with LABA were shown in some studies (86), especially in some subgroups (e.g., African Americans), suggesting a possible role of genetic polymorphisms in mediating adverse effects of beta-agonists (arg-arg polymorphism at position 16 of the beta-

adrenoreceptor) (87). Long-acting beta$_2$ agonist side effects are reduced in association with ICS, leading to consider them as add-on therapy for uncontrolled patients with ICS monotherapy (2, 88). However, whether adding LABA to ICS increases the risk of asthma mortality remains unknown (89).

Furthermore, asthma therapeutic management have considerably evolved over the last twenty years by the disposal of novel treatments particularly inhaled drug combinations and targeted biological therapies (90). Some genetic variants have been associated with response to asthma treatments, suggesting that personalized approach of asthma therapeutic management may maximize therapeutic benefits in the future (91-96). New therapeutic innovations based on monoclonal antibodies already allow or will soon allow to treat specific severe asthma phenotypes. Omalizumab (anti-immunoglobulin [Ig] E) and mepolizumab (anti-interleukin [IL] 5) are the monoclonal antibodies having a marketing authorisation for asthma treatment in France. They are authorized only for asthma refractory to other treatments with either allergy or hypereosinophilia, respectively. Biotherapies could represent the future of asthma therapy. Several medications are being developed, and target mainly signalling pathways involved in inflammation, through IL-2 (e.g., daclizumab), IL-4 (e.g., dupilumab, pascolizumab), IL-5 (e.g., reslizumab, benralizumab), IL-13 (e.g., anrukinzumab, lebrikizumab, tralokinumab), CD4 (e.g., keliximab), tumor necrosis factor α (e.g., golimumab) monoclonal antibodies, and immune allergic mechanisms (e.g., lumiliximab) (51, 97, 98). Targeted therapies have been poorly assessed in the elderly (98). Further research is needed to integrate this new therapeutic management as an integral part of “P4 medicine” (Personalized, Predictive, Preventive, and Participatory) (99).

II. PHARMACOEPIDEMIOLOGICAL APPROACH IN ASTHMA

Pharmacoepidemiology research is a relative recent approach to assess medication effects and their use in real life. Its study design is complementary to that of clinical trials for medication evaluation, particularly in complex chronic diseases such as asthma. However, pharmacoepidemiological methodology is hampered by several challenges, mainly related to the observational nature of the approach.

A. Need for epidemiological approach in asthma drug evaluation

Randomized clinical trials remain the gold standard for providing evidence of medication efficacy and safety in clinical settings (Table I). Clinical benefits of asthma maintenance therapy have clearly been demonstrated in terms of asthma morbimortality by RCT (100). Major impact of RCT is unquestionable to evaluate the beneficial and risk effects of a drug, especially relevant for preapproval trials, before its marketing authorization application or indication extension. These interventional studies provide strong evidence, as they are able to limit bias through the random allocation process and the control of environmental factors during the study. However, their design also leads to some limitations in the external validity of the findings due to: i) the misrepresentation of the target population by a highly selected population with restrictive inclusion criteria, usually excluding vulnerable patient groups, such as elderly patients with multiple comorbidities, children and young women; ii) the highly controlled environment including standardized and optimized use of medications; iii) the short follow-up not allowing to evaluate the long-term effects of chronic drug exposure; iv) sometimes the low number of patients included underrepresenting patient population that will use most of the drugs; v) the lack of follow-up on the evolution of medical practices; and vi) the indirect comparisons of drugs across multiple RCT because of

the non comparison of alternative treatment strategies. Therefore, in the context of chronic diseases affecting large populations of patients with different endo-phenotypes, such as asthma, the strict design of RCT does not allow to reflect all subsets of asthma, limiting their external validity and the generalizability of their results to the whole population. Furthermore, medications have a long life and post-marketing research is needed to assess their safety and long-term efficacy in large populations, and potentially extent their indications.

Table I. Complementarity of randomized controlled trials and pharmacoepidemiology studies in drug evaluation.

Features	Randomized controlled trials	Pharmacoepidemiology studies
Study design	• Interventional studies	• Mostly observational studies
Number of subjects	• Relatively limited number of subjects included	• Large population included
Population selection	• Strong inclusion and exclusion criteria	• Inclusion of "real life" subjects
Study period	• Short follow-up	• Short and long follow-up
Strengths	• Randomization • Group of controls • Strong evidence • Quality of data • Strong phenotypic characterisation of the population	• Unselected population or population selected on a limited number of characteristics • Mid to long-term follow-up possible
Limitations	• External validity related to the strong population selection • Usually do not allow the assessment of the mid to long-term treatment effects	• Possible biases inherent to observational studies: recall bias, confounding/indication/ prothopatic bias, exposure misclassification

The pharmacoepidemiological approach, defined as observational study aiming to address both beneficial and adverse drug effects and their use at the population level, provides

complementary information to RCT (Table I) (101). Its interest was growing over the last decades. It has been shown to be a useful tool to improve the effectiveness and efficiency of healthcare interventions with appropriate methodologies (102). Such improvements are of particular interest in asthma, since limited information on long-term effects of drugs used still exists. Few studies were conducted to assess the long-term benefits of asthma maintenance therapy on respiratory health in adults, especially ICS. A beneficial effect of ICS was suggested on the long-term evolution of lung function among adult patients with asthma (Table II) (103-106). However, prospective pharmacoepidemiological studies relying on large and well-characterized populations are needed to assess the long-term benefits of ICS on respiratory health in asthma.

Table II. Observational studies performed to assess the association between the long-term exposure of inhaled corticosteroids and the lung function evolution in adults with asthma. (103-106)

Author	Journal	Year	Outcome	Study population	Average follow-up	Methods	Main results
Dijkstra et al.	Thorax	2006	Lung function decline	122 subjects with asthma aged from 30 to 45 years at inclusion	23 years	Linear mixed-effects model	Lung function decline was less important in subjects exposed to ICS, as compared to subjects unexposed ($p = 0.03$)
Lange et al.	Thorax	2006	Lung function decline	234 subjects with asthma from CCHS cohort aged at least 30 years at inclusion	10 years	Linear model	As compared to subjects unexposed to ICS, subjects exposed had a decrease of FEV_1 decline with a 18mL/year average reduction ($p = 0.01$)
de Marco et al.	J Allergy Clin Immunol	2007	Lung function decline	667 subjects with asthma from ECRHS study aged from 20 to 44 years at inclusion	9 years	Mixed hierarchical model (two levels)	The use of ICS was associated with a decrease in FEV_1 decline of 11mL/year (trend $p = 0.02$)
Shimoda et al.	Int Arch Allergy Immunol	2013	Lung function decline	167 adults with asthma	15 years	Friedman's test	Lung function decline was less important in subjects regularly exposed to ICS (28.2mL/year), as compared to subjects unregularly exposed (44.6mL/year) ($p <0.05$)

CCHS, Copenhagen City Heart Study; ECRHS, European Community Respiratory Health Survey; FEV_1, Force Expiratory Volume in 1 second; ICS, Inhaled corticosteroids.

B. Methodological challenges in pharmacoepidemiology

Although pharmacoepidemiological studies based on large populations have the advantage of being representative of routine care and can be conducted in a timely manner, they suffer from several methodological issues, which have to be taken into account.

1. Estimation of drug exposure

Assessing drug exposure is one of the cornerstones in pharmacoepidemiology research. Different methods are used to measure the level of drug exposure, such as self-reporting, electronic monitoring and healthcare databases. Missclassification may occur whatever the method used (107-110). Self-reporting may lead to over-reporting but mainly to drug exposure underestimation because of the recall bias and under-reporting. Healthcare databases are also hampered by under- (i.e., other drug sources such as over-the-counter drugs or hospital prescriptions) and over-estimation (i.e., unused drugs prescribed, medications as needed).

Surveys provide information on drug use from subjects themselves. Although home inventories are considered as a gold standard in drug exposure assessment, questionnaires are commonly used as a source of drug exposure and can be the only method to record medication use in many settings (110, 111). Modes of data collection by questionnaire differ in the method of contacting subjects (e.g., face-to-face, telephone contact, letter, email), in the medium of delivering of the questionnaire to respondents (e.g., face-to-face, telephone, paper, electronic support), and in the administration of the questions (i.e., interview or self-administration), both influencing data accuracy and quality (112). A standardized way of asking questions on drug use does not exist and may affect data reliability and validity, and also be variously associated with exposure misclassification. Studies addressing the effect of questionnaire design on the recall of pharmacological treatments are consistent and showed

that drug oriented questions yield higher prevalence of drug utilization than open-ended questions (113). One of the main limitations of questionnaires for drug exposure assessment relies on the limited number of drugs categories evaluated. Questionnaire design also influences recall, especially for self-reporting, and may lead to different estimates on drug exposure (110, 113). Methods for drug utilization data collection are poorly addressed (113). There is not yet a well-designed, validated questionnaire concerning overall drug use for pharmacoepidemiological research in order to compare different settings.

Most of pharmacoepidemiological studies are currently performed using healthcare databases providing information on both drug exposure and health outcomes (102). Claims data, also called billing or sometimes administrative data, represent a powerful resource for healthcare research. Not primarily generated for a purpose of research, they provide a source of large and complex quantitative information about patients, fitting with the definitions of big data. In particular, they contain comprehensive records of patients' healthcare use covering a wide range of data from hospitalization to pharmacies (114). They are widely available in electronic format and ensure free from non-response and dropout. Claims data are considered as a substitute for information contained in patients' medical records. They have been available for many years in some countries, such as Norway, Finland and Sweden (115). In other countries, especially Canada, United States, United Kingdom, and later in France, the relatively recent increased availability of claims data for research represents a step further in clinical and epidemiological studies.

At the population level, drug claims databases offer a useful support to assess individual drug exposure, more or less accurate depending on healthcare system. The French healthcare system ensures an equal access to healthcare for all patients, and provides an exhaustive drug claims database for non-hospital medications prescribed. The databases do not include information on medications ordered on website, over-the-counter medications and

non-subsidized drugs, herbal drugs, drugs used in hospitals or from storerooms, and sometimes used in nursing homes. As self-reporting, medication reimbursement records represent a proxy for medication adherence but might not accurately reflect drug intake, especially in chronic diseases, because of poor adherence and misuse of medical devices, such as in asthma (2, 58, 59, 64, 84). A consistent relationship between inhaler adherence and stronger inhaler-necessity beliefs, and potentially older age, was shown in the literature (84).

Several studies used drug administrative data to describe asthma treatments in real life. An interesting approach using drug administrative database has been developed to assess asthma quality of care. Several asthma medication ratios based on asthma medications dispensed over 12-month periods were proposed (Table III) (116-121). Recently, the controller-to-total asthma medication ratio, defined as the ratio of the number of ICS and LTRA units dispensed under the total R03 ATC (Anatomical Therapeutic Chemical) drugs dispensed, was proposed (121). All of asthma medication ratios, mainly studied in the US population, have the ability to predict short-term asthma-related outcomes (i.e., emergency department visit, hospitalization, asthma exacerbations…) among children and adults with asthma. However, such quality of care markers might behave differently in other countries with different healthcare system, or with old age and/or gender. Moreover, beside their estimated values at a single time point, it is not known to which extent their long-term fluctuations are useful to predict asthma-related outcomes.

Claims data provide a wide range of information on drug prescriptions but very few additional information are available (e.g., individual and phenotypic characteristics). Information such as the indication of use or the extent to which patients consume the drugs will remain largely unknown and it should be noted that all these units represent approximate estimate of true consumption (122). Data from general practitioner records can be more informative about indication for drug prescriptions, diagnoses and other health-related data,

although these records are not always consistently completed (113). More and more healthcare researches perform data or source linkage, defined as “a process of pairing records from two files and trying to select the pairs that belong to the same entity” (123), of several different databases to enhance existing data and provide a more comprehensive range of individual information. However, the major challenges in data linkage are the access to datasets, which might take months or years, and linkage quality when both datasets do not include an identical identification variable. Studies combining detailed questionnaires and direct access to drug claims data are highly valuable to assess treatment effects in real life.

Table III. Epidemiological studies using drug administrative data to assess asthma medication ratio. (116-121)

Author	Journal	Year	Population	Ratio	Outcomes	Main results
Schatz et al.	Chest	2005	109,774 subjects with asthma aged 5 to 56 years	Source: Pharmacy claims data Definition: (Units of controllers) / (units of controllers + relievers) Period of calculation: 12 months Cut-off: 0.3 and 0.5	Asthma emergency department visit or hospitalization	An asthma medication ratio ≥ 0.5 was suggested to be the best quality-of-care marker.
Schatz et al.	Chest	2006	2,250 subjects with asthma aged 18 to 56 years	Source: Pharmacy claims data Definition: (Units of controllers) / (units of controllers + relievers) Period of calculation: 12 months Cut-off: 0.5	Asthma quality-of-life, asthma control, symptom severity, asthma emergency department visit or hospitalization	A higher asthma medication ration was associated with better asthma-related outcomes.
Schatz et al.	Ann Allergy Asthma Immunol	2008	360,975 subjects with asthma aged 5 to 56 years	Source: Pharmacy claims data Definition: (Units of controllers) / (units of controllers + relievers) Period of calculation: 12 months Cut-off: 0.5	Asthma emergency department visit or hospitalization, asthma exacerbation	The asthma medication ratio with at least 4-medication dispensing was recommended.
Broder et al.	Am J Manag Care	2010	38,538 subjects with persistent asthma aged 5 to 56 years	Source: Pharmacy claims data Definition: (Units of controllers) / (units of controllers + relievers) Period of calculation: 12 months Cut-off: 0.5	Patients characteristics (sociodemographic, level of asthma treatment, adherence, comorbidities)	A high ratio was associated with greater adherence to therapy and association of maintenance therapy.

Andrews et al.	Medicare Medicaid Res Rev	2013	19,512 subjects aged 2-18 years from South Carolina Medicaid recipients	Source: Health insurance database Definition: [number of controller fills / (number of controller fills + number of short-acting beta-agonist fills)] Period: 12 months Cut-off: 0.5	Asthma related emergency department visits, hospitalisations, and a combined outcome of emergency department visit or hospitalisation in the subsequent 3, 6, and 12 month time periods	Asthma medication ratio using a 0.5 cut-off was a significant predictor of ED visits and hospitalisations in children.
Laforest et al.	Eur Respir J	2014	2,162 subjects aged 13 to 40 years from the Permanent Sample of Health Insurance Beneficiaries (EGB), a 1/97th random sample of the French National Claims Data Beneficiaries	Source: Health insurance database Definition: ICS/R03 and (ICS+LTRA)/R03 Period: 12 months Cut-off: 0.5	OCS as proxy for asthma exacerbations Annual number of visits to a family physician Hospitalisation for asthma	Subjects with high ratios received less OCS and had fewer asthma-related hospitalisations whatever the ratio considered.

ICS, Inhaled corticosteroids, LTRA, Leukotrien receptor antagonists; OCS, Oral corticosteroids; R03, Drugs for obstructive airway diseases according to the Anatomical Therapeutic Chemical classification.

2. Taking into account the indication bias: the counterfactual approach

Pharmacoepidemiological research is mostly based on observational studies in which the causal link between medications and health may be discussed. In observational studies, medication use is not randomized but often influenced by patients' baseline characteristics (e.g., the most severe patients are the most treated) (124). When one (or more) of these features is also related to the outcome, it is a confounding factor leading to a systematic error in treatment effect estimate, called the indication bias. A significant difference in the outcome can be observed, even in the absence of treatment effect, and reflect only the heterogeneity of patients' characteristics between the exposed and unexposed groups that are compared. This difference in the baseline characteristics distribution leads to bias in exposure effect estimate, and conventional statistical methods (adjusted for known confounders, stratification or matching) have several limitations to reduce this bias (complexity of calculation based on the number of variables and exposure categories, model specification, insufficient number of events per covariate, change in effect), and so to estimate the causal relationship of the treatment on health (125).

Several causal analysis methods were developed to take into account the causal link between exposure and outcome, including graphical analysis (e.g., Rothman's model, acyclic directed graph), path analysis (e.g., structural equation model, dynamic path analysis), and counterfactual analysis (e.g., propensity score method, marginal structural model) (126). The propensity score method is a counterfactual approach used more and more in pharmacoepidemiology. It was proposed by Rosenbaum and Rubin in 1983 as an adjustment method that models the relationship between treatment and subjects' characteristics in order to establish a posteriori groups of subjects with similar baseline characteristics and differing only in exposure level (Figure 6) (127).

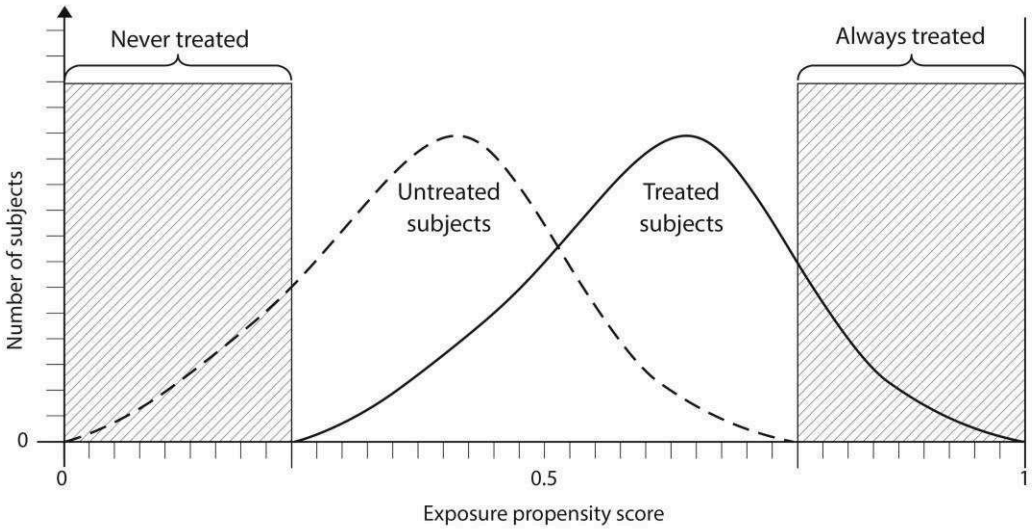


Figure 6. Regions of non-overlap of the exposure propensity score distributions of two treatment groups. Adapted from (128)

The propensity score is a single variable, function of covariates, which summarizes the baseline characteristics related to treatment indication (information condensation). For the subject i, the propensity score is the probability of receiving the studied treatment (Z = 1) given his baseline characteristics (X_i): $e(x_i) = p(Z_i = 1 \mid X_i = x_i)$ (129). For a value of $e(x_i)$, the exposed and unexposed subjects have on average the same characteristics at baseline. The construction of the propensity score is based on the strongly ignorable treatment assignment assumption, i.e., all confounding variables must be identified so that treatment exposure is independent conditionally to subjects' baseline characteristics (129). Its construction is largely carried out by logistic regression in which the exposure and subjects' baseline characteristics are the dependent and independent variables, respectively. The strength and the performance of the propensity score method are largely based on data quality. The selection method of variables to include in the model is discussed in the literature. The aim is to balance the distribution of confounding factors (i.e., reduce the estimation bias of the treatment effect) and not to predict treatment decision. The statistical significance is not a required condition for the inclusion of covariates in the propensity score model (130). Using a

model selection algorithm (univariate and multivariate analysis) may exclude variables of interest and select only variables related to exposure, increasing the imprecision in estimating exposure effect (125, 131). In this context, it seems, however, more important to include variables closely related to health outcome(s), but with a weak relationship with treatment decision (131). Although the use of propensity score in pharmacoepidemiological studies has increased in recent years (132), it is not clear if this approach provides consistently better estimates of medication effects compared to those obtained from conventional statistical methods (133).

3. Taking into account missing data

Missing data are a major challenge in research, including in epidemiological studies (134, 135). The rate of missing data varies widely among studies, but 95% of datasets contain at least one missing data. A high proportion of missing data may lead to bias and decreased statistical power. Little and Rubin introduced in 1976 a classification of missingness according to their distribution, probability and pattern (136). An exploratory analysis of missingness has to be performed to properly take into account missing data in statistical analysis, including first a detailed descriptive analysis: proportion of subjects with complete data (number of subjects with missing data / whole study population), proportion of variables with complete data (number of variables with missing data / total number of variables), and proportion of missing observations (number of missing data / total number of observations). The pattern of missing data has to be assessed: i) missing completely at random (MCAR), defined as the propensity for a data to be missing is not related to any observed or missing data; ii) missing at random (MAR), defined as the propensity for a data to be missing is related to some observed data but not to missing data; and iii) missing not at random (MNAR), defined as the propensity for a data to be missing depends on the other missing data. When analysing longitudinal data, the monotone pattern (i.e., when data is missing at a

certain measurement time for a subject, data are also missing for this subject at all following measurement times) or non-monotone pattern (i.e., data are missing at any time for a subject but are observed at previous and posterior times) has to be determined for each missing variable.

Several methods have been proposed in the literature to take into account missing data, such as complete case analysis, generalized propensity score or multiple imputation. Multiple imputation is the most effective and easiest method to take into account missing data (Figure 7) (137).

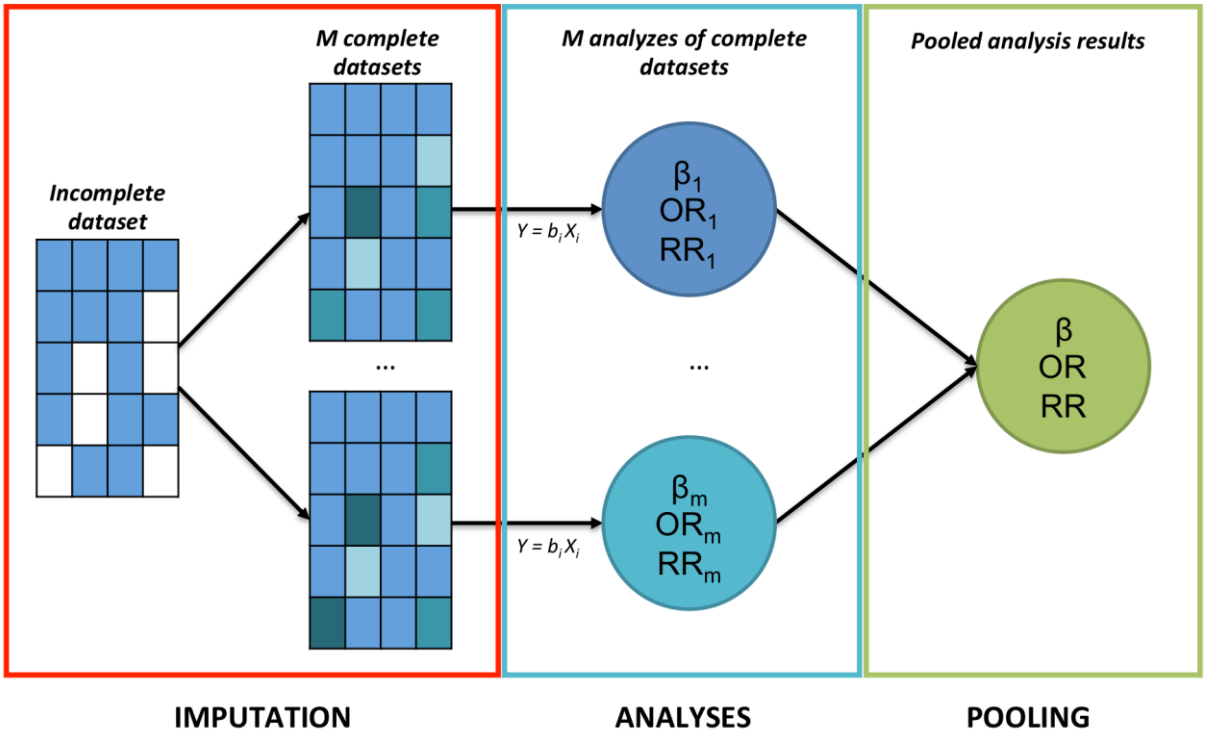


Figure 7. Description of multiple imputation method.

Multiple imputation implies two assumptions (138): i) proper multiple imputation, i.e., the method incorporates adequate variability among the n imputation sets to ensure adequate inference, and ii) missing data are MAR. Imputation is performed using information from variables associated with the variable to be imputed. Several methods are available for

variable imputation according to their type (i.e., qualitative or quantitative variable) and pattern (i.e., monotone or non-monotone) (Table IV). The imputation of missing categorical data with non-monotone pattern is more difficult. The use of expectation-maximization algorithm seems to provide an unbiased estimate of this type of parameters (139). The number of imputations is also discussed in the literature. Although the multiple imputation theory suggests a small number of imputations (3-5), more imputations are recommended to ensure a sufficient statistical power (140).

Table IV. Statistical methods used to impute variables according to their quality and pattern of missingness.

Pattern of missing data	Quality of variables to impute	Recommendations
Monotone	Continuous	Linear regression
		Predicted mean matching
		Propensity score
	Discrete (ordinal)	Logistic regression
	Discrete (nominal)	Discriminant function method
Non monotone	Continuous	Markov chain Monte Carlo full-data imputation
		Markov chain Monte Carlo monotone-data imputation

III. OBJECTIVES OF THIS THESIS

The literature review presented above highlights that although asthma is a known heterogeneous chronic respiratory disease affecting many people and whose therapeutic management is standardized by international guidelines, research on long-term benefits of asthma maintenance therapies is particularly needed. In the context of population ageing and lack of specific therapeutic management guidelines, asthma in the elderly remains an issue of interest still poorly addressed. The development of tools to identify or predict subjects poorly controlled would be valuable in the development of epidemiological surveillance by drug claims data. Comorbidities are common in advanced age. Few studies assessed the relationship between asthma-related comorbidities and asthma, particularly the impact of polymedication on asthma characteristics.

The objective of this thesis was to add information on the assessment of the quality of asthma therapeutic management in real life, using pharmacoepidemiological tools. Specific aims were to investigate: i) the long-term benefits of inhaled corticosteroids in asthma, ii) the controller-to-total asthma medication ratio and its fluctuations over time in the elderly, and iii) the polymedication in elderly asthma.

IV. STUDY DESIGN

A pharmacoepidemiological approach was conducted in two complementary French epidemiological studies, each initiated for over 20 years to meet the objectives of this thesis: the EGEA study, a study focused on respiratory health, and the E3N study, a prospective study including 98,995 women from 1990 onwards (Table V).

The EGEA study (PI: Francine Kauffmann up-to 2013 and then Valérie Siroux) is a French multicentre longitudinal study (Paris, Lyon, Marseille, Montpellier and Grenoble) focused on respiratory health (15, 141, 142). Overall 2,120 participants with asthma recruited in chest clinics, their first-degree relatives and controls have been included in the study, especially 904 participants with asthma, for which a detailed phenotypic characterization is available. The EGEA study is composed of two follow-ups (EGEA 2 and 3). Each survey included a questionnaire on asthma based on standardized questionnaires already used in international studies, and a questionnaire on asthma medications especially detailed for the last two surveys. The protocol involved at EGEA 1 and 2 clinical, respiratory and biological examinations. Data quality offered the opportunity to study the long-term effects of ICS on respiratory health (asthma control, lung function evolution) and quality of life. However, the relatively small number of participants with asthma included and the lack of drug claims data in this study limited to further expand the research area on these data. Thus, to develop my pharmacoepidemiological project on asthma, access to data from the E3N study, a large prospective study including drug claims data, was obtained.

Table V. Description of EGEA and E3N studies.

Study name	Etude épidémiologique des facteurs Génétiques et Environnementaux de l'Asthme, l'hyperréactivité bronchique et l'atopie / Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy	E3N ETUDE EPIDEMIOLOGIQUE AUPRES DE FEMMES DE LA MGEN
Study design	Longitudinal multicenter study among subjects with asthma, their first-degree relatives and controls (Paris, Lyon, Marseille, Montpellier, Grenoble)	Women belonging to MGEN, a French national health insurance plan covering mostly teachers (metropolitan France)
Study population	2,120 children and adults from 7 to 70 years at baseline	98,995 women from 40 to 65 years at baseline
Follow-up	1991-2012 : ↳ EGEA1 : 1991-1993 (n = 2,047) ↳ EGEA2 : 2003-2007 (n = 1,903; response rate = 91%) ↳ EGEA3 : 2011-2013 (n = 1,558; response rate = 79%)	1990-2011 : ↳ Questionnaire every two years (overall 9 questionnaires) ↳ Response rate for all questionnaires >80%
Number of participants with ever asthma	904 at baseline	7,100 (1990 à 2010)
Drug data	Detailed questionnaires at EGEA2 and EGEA3	- Drug claims data (MGEN) from 2004 onwards - Detailed questionnaire (Asthma-E3N study, 2011-2012)
Individual and phenotypic characteristics	- Detailed questionnaires on respiratory health, environment and quality of life - Examination at EGEA1 and EGEA2 (spirometry, broncial hyperresponsiveness texploration, skin tests, complete blood count, total IgE, condensate and exhaled NO) - Wide biobank and genome-wide data	- Detailed questionnaires on health (including asthma) and environment - Detailed questionnaire on respiratory health and quality of life (Asthma-E3N study, response rate : 94.7%)

The E3N study (PI: previously Françoise Clavel-Chapelon and now Marie-Christine Boutron-Ruault) is a French prospective study conducted on the role of diet and hormonal factors on cancer onset (143). It is the French component of the European Prospective Investigation into Cancer and Nutrition study, coordinated by the International Agency for Research on Cancer. The E3N study initiated in 1990 includes 98,995 French women belonging to a national health insurance plan (MGEN) covering mostly teachers, aged 40-65 years at baseline. Respiratory health data have been available since 1992. From 1992 to 2000, a single and repeated question was asked to all women ("Have you ever had asthma

attacks?"). Detailed questions from international tools (BMRC/ECSC; American Thoracic Society; questions from the ECRHS; and the frequency of asthma attacks in the previous 12 months before questionnaire) were introduced in questionnaires from 2002 onwards. Furthermore, the Asthma-E3N study (PI: Raphaëlle Varraso), a nested case-control study within the E3N study, was conducted in 2011-2012 among the 7,100 women with asthma and 14,200 randomly selected aged-matched women without asthma to improve the phenotypic characterization of asthma (11). A self-administrated questionnaire on respiratory health close to the EGEA study questionnaire, including the ACT and the asthma quality of life questionnaire (AQLQ), was used. In addition to detailed questionnaires, reimbursements for non-hospital medications have been comprehensively collected from the MGEN database for each subject since 2004. Interestingly, a strong concordance on asthma medication exposure between data collected by questionnaire and the MGEN database has been shown (Sanchez et a1, personal communication).

CHAPTER II

LONG-TERM BENEFITS OF INHALED CORTICOSTEROIDS IN ASTHMA: THE PROPENSITY SCORE METHOD

Long-term benefits of inhaled corticosteroids in asthma: the propensity score method

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Abstract

Purpose: The aim of this study was to apply a propensity score approach to assess the long-term benefits of inhaled corticosteroids (ICS) on respiratory health in asthma.

Methods: This analysis was conducted on adults with persistent asthma from the Epidemiological study on the Genetics and Environment of Asthma (EGEA), a 12-year follow-up study. ICS exposure was assessed by questionnaire. Change in lung function over the follow-up period, asthma control and health-related quality of life (asthma quality of life questionnaire) were assessed by standardized and validated methods.

Results: Among 245 adults with persistent asthma, 78 (31.8%) were regularly/continuously exposed to ICS (≥6 months/year, ICS_{++}) and 167 never/irregularly exposed to ICS (<6 months/year, $ICS_{+/-}$) over the follow-up period. Compared to $ICS_{+/-}$ subjects, a non-significant trend for a slower lung function decline (mL/year) was observed in ICS_{++} subjects (β [95%CI] = -11.4 [-24.9; 2.0]). The ICS_{++} subjects did not have better controlled asthma and higher health-related quality of life as compared to $ICS_{+/-}$ subjects.

Conclusions: Applying a propensity score method did not offer evidence of a statistical significant long-term benefit of ICS on respiratory health in adults with persistent asthma regularly or continuously exposed to ICS over a long period.

Key words: propensity score; indication bias; asthma; inhaled corticosteroids; long-term effects; respiratory health; pharmacoepidemiology.

Key points

- This is one of the first attempts in the literature at the correction for the indication bias in the assessment of long-term asthma medication effects in an observational study.
- This study highlights the potentials and limitations of counterfactual methods to assess long-term effects of asthma maintenance therapies in an epidemiological cohort.
- Further pharmacoepidemiological studies are needed to estimate the long-term effects of inhaled corticosteroids in asthma in the general population.

Introduction

Observational studies complement randomized clinical trials by assessing treatment effects in larger and more diverse populations and by using longer follow-up periods (114). A major challenge in conducting epidemiological studies is to account for confounding by indication that is a bias commonly encountered in the assessment of treatment effects from observational studies (144). To reduce confounding by indication, the propensity score, a method based on the counterfactual approach to causality, has been proposed as an effective way to reduce covariate imbalance between comparison groups, recreating the conditions of a quasirandomized experiment in observational studies (129). This statistical approach has been increasingly used in epidemiological studies for a variety of health outcomes, but its application in asthma pharmacoepidemiology research is scarce (145).

Asthma is a major public health problem given its high prevalence, associated morbi-mortality and economic burden (20, 146, 147). Asthma management is based on inhaled corticosteroids (ICS) that are the cornerstone of asthma maintenance therapy, associated or not with long acting β_2-agonists or leukotriene modifiers (147). Although a large number of

randomized clinical trials have established evidence that maintenance therapy reduces acute asthma exacerbation events in patients with persistent asthma, a recent study based on a propensity score approach was unable to show any benefit among children and young adults with asthma (145). The efficacy of ICS in long-term prevention of hospitalization and mortality has been reported in epidemiological and country-based studies (148-150). Three observational studies, which did not use a counterfactual approach to take into account indication bias, have reported an association between long-term ICS exposure and the evolution of lung function in adults with asthma (103, 104, 151).

The aim of this study was to apply a propensity score approach in adults with persistent asthma participating in a well-characterized epidemiological cohort, i) to evaluate this method's ability to characterize the long-term benefits of ICS on lung function evolution, ii) and to assess their efficacy on asthma control and health-related quality of life (HRQL).

Methods

Population

This analysis was conducted on adults with persistent asthma from the French longitudinal EGEA study (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy), investigating the same subjects 12 years apart. Protocol and descriptive characteristics have previously been published (website: https://egeanet.vjf.inserm.fr/) (see Supplemental material, p. 81) (141, 142). Briefly, EGEA is a case-control and family study of 2,047 subjects recruited in 1991-1995 (EGEA1) and followed-up for almost 12 years (EGEA2; 2003-2007). Asthma was defined either by a positive answer to one of the two questions at EGEA1 or 2: "Have you ever had attacks of breathlessness at rest with wheezing?" and "Have you ever had asthma?", or being recruited as asthma cases in chest clinics at baseline (141). Subjects were considered with persistent

asthma if they had current asthma, defined by the report of either asthma attacks or respiratory symptoms or asthma treatment in the last 12 months, both at EGEA1 and 2 (152, 153).

Definition of long-term inhaled corticosteroid exposure

Long-term ICS exposure was assessed by questionnaire. At EGEA2, information on ICS use since the past survey was recorded. Data were combined to estimate the average use of ICS between EGEA1 and 2, expressed in months/year for each subject. A subject was defined to be exposed to ICS at least 6 months/year if he had used ICS at least 6 months every year during the follow-up period (EGEA1 to EGEA2).

Outcomes

Lung function evolution. The forced expiratory volume in 1 s (FEV_1) was measured at baseline and follow-up, according to the American Thoracic Society criteria (154). To account for the lung function evolution over life (e.g., the follow-up of the younger subjects includes the "plateau" phase), FEV_1 was not only expressed in milliliters (mL) but also as the percent of the predicted values, using Stanojevic's equations (155). Lung function evolution during the follow-up, expressed either in change in FEV_1% predicted/year or change in FEV_1 in mL/year, was computed as the difference between lung function values measured at EGEA1 and 2 (EGEA1 – EGEA2), divided by the individual duration of follow-up (i.e., a positive value represents a lung function decline).

Asthma control. A multidimensional approach based on combined responses to EGEA2 survey questions was used to approximate as closely as possible the definition of asthma control as defined in the GINA (Global Initiative for Asthma) 2006 guidelines (see Supplemental material, p. 81) (152).

Health-related quality of life. Health-related quality of life was assessed at EGEA2 by the asthma quality of life questionnaire (AQLQ), an asthma-specific instrument that consists of 32 questions, relating to the past two weeks and covering four domains ("symptoms", "activity limitation", "emotional function", and susceptibility to "environmental exposure") (156). The overall AQLQ score was computed as the mean of all 32 questions on the seven-point scale (1 = severely impaired; 7 = not impaired at all), with lower scores indicating worse HRQL. The minimal clinically important difference, which is the smallest difference considered clinically and socially relevant, is 0.5 (157). As previously used in the literature, the HRQL score differences were compared to the minimal clinically important difference when addressing the magnitude of the differences observed between groups (133).

Determinants of inhaled corticosteroid use

Potential determinants of ICS use were selected from the literature and the available data at EGEA1. Socio-demographic characteristics included: age, sex, body mass index, and occupational status. A four-class occupational status (unemployed, executive, technician, and worker) based on the best occupation over life was used. Active and passive smoking exposure was defined by questionnaire in three categories: (i) never/ex-smoker unexposed to passive smoking; (ii) never/ex-smoker exposed to passive smoking; and (iii) active smoker. Asthma characteristics taken into account at baseline were age at asthma onset, an asthma symptom score (defined by the sum of positive answers to five questions related to symptoms in the last 12 months) (158), severity of asthma (defined by the severity and frequency of symptoms and grouped into four classes ranging from 0 to ≥3, with higher scores representing severe asthma) (159), and parental history of asthma. Asthma-related characteristics and rhinitis comorbidity were studied. Bronchial hyperresponsiveness was defined as a 20% fall in FEV_1 for a 4 mg cumulative dose of methacholine in subjects with normal baseline lung function (FEV_1 >80% predicted, best FEV_1 post-diluent >90% of the best initial FEV_1). The

allergic status was assessed by the responses to skin tests to 11 aeroallergens (at least a positive skin test with a wheal diameter ≥3 mm) and total IgE (threshold: 100 UI/L). Hypereosinophilia was defined as a blood level >250 mm^3. The rhinitis and eczema status, commonly associated with atopic asthma phenotypes, were also studied.

Strategy of analysis

Propensity score approach. A single generic-outcome propensity score model was generated under the strongly ignorable treatment assignment assumption (i.e., conditional independence between treatment assignment and potential outcomes given the covariates). A logistic regression model was constructed to predict ICS exposure according to a limited number of covariates (to keep an exposure covariate ratio >8-10) shown to be strongly related to at least one of the health outcomes of interest in the literature and measured before the beginning of treatment exposure, regardless of the statistical significance in our data. The variance inflaction factor, indicator of the multicolinearity between the covariates, was estimated to assess the stability of the model. The adequacy of the model was approached by the following: (i) the c-index (area under the receiver operating characteristic curve); (ii) the Hosmer-Lemeshow goodness-of-fit test, which appraise, respectively, the discrimination and the calibration of the propensity score; and (iii) the balance of covariates between the two groups of ICS exposure within quintile stratification of the score (133).

Estimating propensity scores with incomplete data. Although a low proportion of missing data was observed in our study (4.0%), a multiple imputation (i.e., five simulations) was performed to handle missing background data in the estimation and the use of the propensity scores (see Supplemental material, p. 81) (139, 160).

Statistical analysis. Comparisons of socio-demographic, clinical, biological and lung function characteristics between the two groups of long-term ICS exposure were analyzed by Student's

t-tests for quantitative variables and chi-square tests for categorical variables. Three models were performed in this analysis: unadjusted model, conventional adjusted model, and model using the propensity score method. Estimates from these models were compared. Long-term benefits of ICS were assessed from regression models: linear regression for lung function evolution (a negative beta value means that ICS exposed subjects showed a slower lung function decline over time, as compared to the unexposed group), logistic regression for asthma control (partly-controlled/uncontrolled vs. controlled), and linear regression with a robust estimate of the standard errors for HRQL. The propensity scores were incorporated as the inverse probabilities treatment weighting (IPTW). A sensitivity analysis was performed by selecting subjects continuously and never exposed to ICS between EGEA1 and 2 to increase the contrast of exposure. All analyses were performed using the SAS 9.3 statistical software (SAS Institute, Cary, NC, USA).

Results

Study population

This analysis was conducted on 245 adults with persistent asthma, recruited at EGEA1 and followed-up at EGEA2, with sufficient data to assess asthma treatment use (Figure 8). The mean age of the population at baseline was 38.5 years, and the sex ratio (Male/Female) 1.1 (Table VI).

On the basis of the long-term ICS exposure distribution in our population, two groups were identified: 78 subjects regularly or continuously exposed to ICS (i.e., ≥6 months/year) between EGEA1 and 2 (ICS_{++}), and 167 never or irregularly exposed to ICS (i.e., <6 months/year) ($ICS_{+/-}$) over the entire follow-up period (11.5 years on average) (Figure 9). Compared to $ICS_{+/-}$ subjects, ICS_{++} subjects were significantly older (43.7 ± 13.7 vs. 36.1 ±

13.1, p <0.0001), had more severe asthma (p = 0.003), lower FEV_1% predicted (78.1 ± 20.0 vs. 91.9 ± 17.2, p <0.0001), and higher blood eosinophilia level (60.3% vs. 45.2%, p = 0.03).

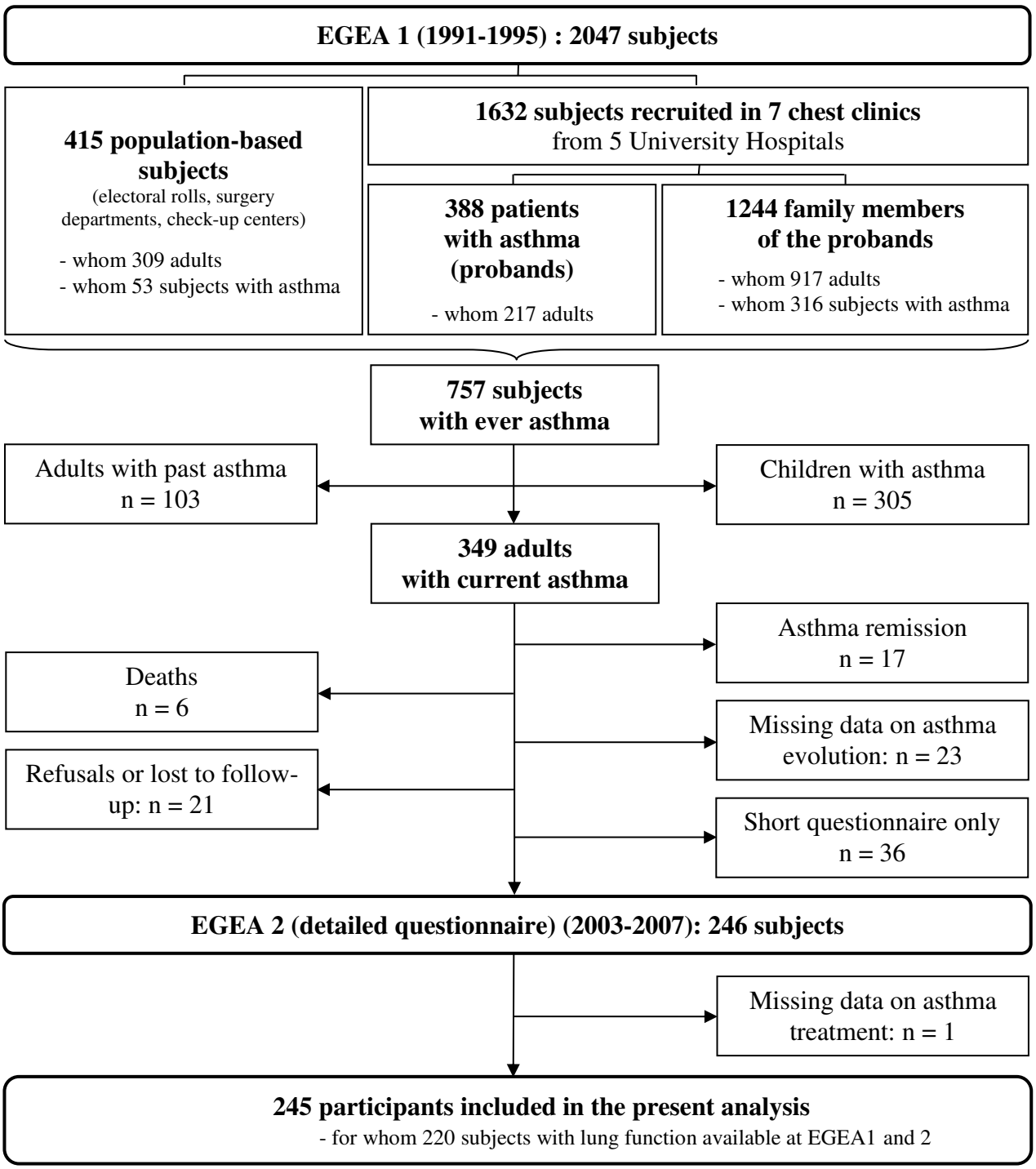


Figure 8. Flowchart of the participants included in this analysis from the Epidemiological study in the Genetics and Environment of Asthma (EGEA).

Table VI. Characteristics of the population at baseline (Epidemiological study in the Genetics and Environment of Asthma (EGEA) 1) according to the level of long-term inhaled corticosteroid exposure.

Variable		Whole population (n = 245)	ICS_{++} (n = 78)	$ICS_{+/-}$ (n = 167)	p value
Socio-demographic characteristics					
Age (years), mean ± SD		38.5 ± 13.7	43.7 ± 13.7	36.1 ± 13.1	<0.0001
Male, %		52.6	53.8	52.1	0.80
BMI (kg/m²), %	<18.5	9.8	9.0	10.2	0.46
	18.5≤ BMI <25	48.6	55.1	45.5	
	25≤ BMI <30	27.7	21.8	30.5	
	≥30	13.9	14.1	13.8	
Occupational, %	Unemployed	16.0	15.4	16.3	0.71
	Executive	31.5	35.9	29.4	
	Technician	39.1	34.6	41.2	
	Worker	13.4	14.1	13.1	
Environment					
Smoking, %	Never/ex-smoker and ETS -	57.4	65.3	53.7	0.17
	Never/ex-smoker and ETS +	26.4	24.0	27.5	
	Current smoker	16.2	10.7	18.8	
Asthma					
Age at asthma onset (years), %	≤4	20.0	24.4	18.0	0.06
	4< age ≤16	30.6	20.5	35.3	
	>16	49.4	55.1	46.7	
Asthma symptoms, %	0	9.0	4.2	11.2	0.01
	1	13.0	11.3	13.8	
	2	18.9	12.7	21.7	
	3	27.3	23.9	29.0	
	4	26.0	36.6	21.0	
	5	5.8	11.3	3.3	
Asthma severity, %	Grade 0	30.8	14.7	38.4	0.003
	Grade 1	22.0	28.0	19.2	
	Grade 2	19.2	19.1	19.2	
	Grade ≥3	28.0	38.2	23.2	
Parental asthma, %	None	59.7	64.4	57.5	0.61
	Father	21.0	20.5	21.2	
	Mother	12.0	11.0	12.5	
	Both	7.3	4.1	8.8	
Asthma related phenotypes					
FEV_1 (L), mean ± sd		3.09 ± 0.94	2.59 ± 0.81	3.33 ± 0.90	<0.0001
FEV_1% predicted, mean ± sd		87.5 ± 19.2	78.1 ± 20.0	91.9 ± 17.2	<0.0001
Bronchial hyperresponsiveness (PD_{20} >4 mg), %		78.8	78.3	79.0	0.57
≥1 positive skin prick test, %		71.2	68.1	72.6	0.48
Total IgE ≥100 UI/L, %		69.0	66.7	70.1	0.60
Blood eosinophilia >250 mm^3, %		50.0	60.3	45.2	0.03
Rhinitis, %		70.9	74.4	69.3	0.41
Eczema, %		43.0	46.1	41.6	0.50

BMI, Body Mass Index; ETS, Environmental Tobacco Smoke; FEV_1, Forced Expiratory Volume in 1 s; ICS, inhaled corticosteroids; $ICS_{+/-}$, subjects never or irregularly exposed to ICS (i.e., <6 months/year) between EGEA1 and 2; ICS_{++}, subjects regularly or continuously exposed to ICS (i.e., ≥6 months/year) between EGEA1 and 2; SD, standard deviation.

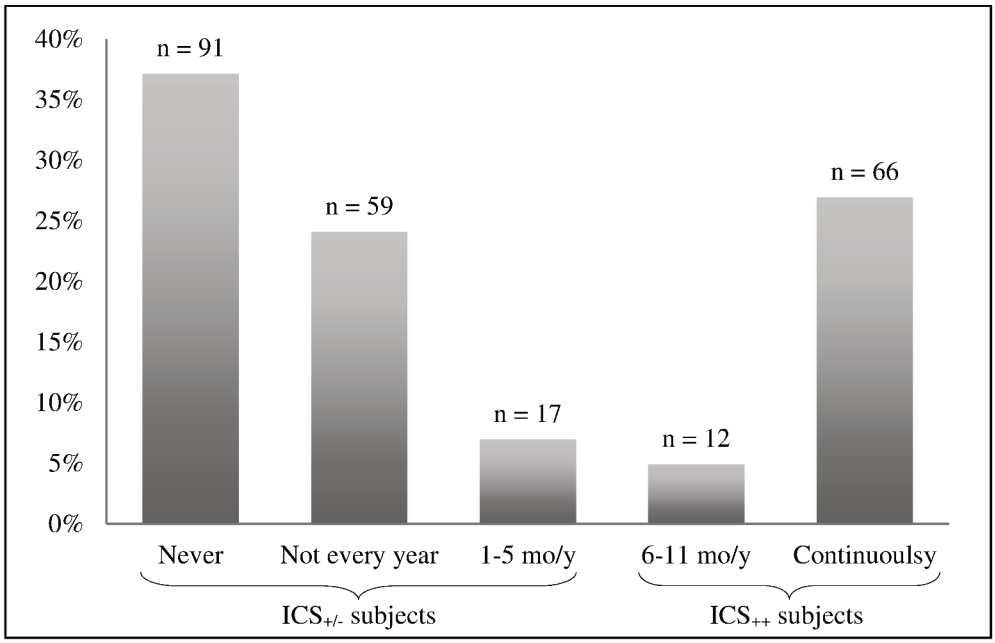
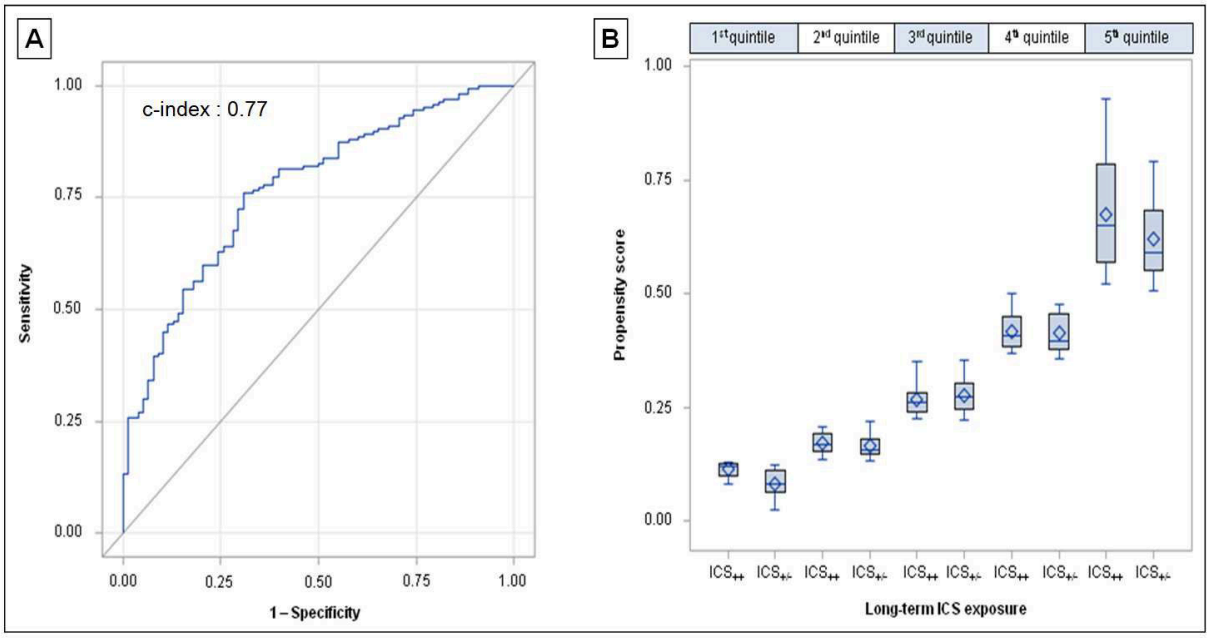


Figure 9. Distribution of inhaled corticosteroid (ICS) exposure between Epidemiological study in the Genetics and Environment of Asthma 1 and 2 among the participants included in this analysis (n = 245).

Propensity score modeling

Eight baseline variables predicting ICS exposure between EGEA1 and 2 were included: age, sex, occupational status, smoking status, age at asthma onset, severity of asthma, FEV_1% predicted (except for lung function evolution analysis which included baseline FEV_1 [over fitting]), and skin prick tests. No multicolinearity was present between the determinants of the model, and no key interaction term was retained in the model.

The propensity score model showed fair discrimination between ICS_{++} and $ICS_{+/-}$ subjects (c-index: 0.77) (Figure 10A). The Hosmer-Lemeshow goodness-of-fit (χ^2 = 4.5, 8 degrees of freedom, p = 0.80) indicated a well-calibrated model. Stratification by quintile showed an overlap of the propensity scores between ICS_{++} and $ICS_{+/-}$ subjects within each stratum (Figure 10B). Similar results of the adequacy of the model were found by conducting a sensitivity analysis on each simulation (n = 5).



ICS, inhaled corticosteroids; $ICS_{+/-}$, subjects never or irregularly exposed to ICS (i.e., <6months/year) between EGEA1 and 2; ICS_{++}, subjects regularly or continuously exposed to ICS (i.e., ≥6 months/year) between the EGEA1 and 2.

Figure 10. (A) Adequacy of the propensity score model assessed by the c-index and (B) the balance of covariates between subjects regularly or continuously exposed to ICS (i.e., ≥6 months/year) and subjects never or irregularly exposed to ICS (i.e., <6 months/year) between Epidemiological study in the Genetics and Environment of Asthma 1 and 2 within quintile stratification of the score.

Long-term effects of inhaled corticosteroids on respiratory health and health-related quality of life

At follow-up, 37.5%, 32.6% and 29.9% of the population had controlled, partly controlled and uncontrolled asthma, respectively. Lung function evolution showed a trend for a decline in FEV_1% predicted/year (mean ± standard deviation [SD] = 0.13 ± 1.21), with an average FEV_1 decline (mean ± SD) estimated at 27.5 ± 43.0 mL/year between EGEA1 and 2. The mean (± SD) total AQLQ score was 5.9 ± 0.9.

In the unadjusted model, the mean (± SD) decline in FEV_1% predicted/year was -0.01 ± 1.56 in ICS_{++} subjects and 0.19 ± 1.00 in $ICS_{+/-}$ subjects (23.3 ± 52.6 and 29.5 ± 37.7 mL/year, respectively). After applying the propensity score method, as compared to $ICS_{+/-}$

subjects, ICS_{++} subjects tended to have a slower lung function decline, expressed as FEV_1% predicted/year (β [95%CI] = -0.31 [-0.67; 0.06]; no statistical difference) and FEV_1 change in mL/year (β [95%CI] = -11.4 [-24.9; 2.0]) (Table VII). The ICS_{++} subjects had more often partly controlled/uncontrolled asthma (odds ratio [95%CI] = 2.77 [1.74; 4.41]) and a lower overall AQLQ score (β [95%CI] = -0.36 [-0.62; -0.10]), compared to $ICS_{+/-}$ subjects at follow-up (Table VII). When comparing the magnitude of the estimates between the propensity score model and the conventional adjustment method, small variations were observed for the FEV_1 evolution and asthma control, but higher variations (sometimes a twofold difference) were observed for the AQLQ scores (Table VII). Nevertheless, no clinical difference was reached for any AQLQ domain both with the propensity score and the conventional adjustment models.

The sensitivity analysis conducted on a more contrasted population as regards to ICS exposure (66 subjects continuously exposed, ICS_{+++}, and 91 never exposed, ICS_{-}), showed a comparable lung function decline between ICS_{+++} and ICS_{-} subjects by the propensity score method and by the conventional adjustment model. The ICS_{+++} subjects had more often partly controlled/uncontrolled asthma and a lower overall AQLQ score, compared to ICS_{-} subjects for both methods (see Table S1 in Supplemental material, p. 82).

A sensitivity analysis to account for the family design of the EGEA study, conducted on a restricted population including a single randomly selected subject per family (n = 222), led to the same conclusions (data not shown).

Table VII. Effects of the long-term inhaled corticosteroid exposure on lung function evolution, health-related quality of life, and asthma control at Epidemiological study in the Genetics and Environment of Asthma (EGEA) 2 assessed using different adjustment models.

	Unadjusted model			Propensity score model *			Adjusted model †		
	β	95%CI	p value	β	95%CI	p value	β	95%CI	p value
FEV_1 evolution									
Change in FEV_1% predicted/year									
ICS_{++} vs. $ICS_{+/-}$	-0.21	-0.55; 0.13	0.23	-0.31	-0.67; 0.06	0.10	-0.26	-0.66; 0.13	0.18
Change in FEV_1 (mL/year)									
ICS_{++} vs. $ICS_{+/-}$	-6.2	-18.3; 5.8	0.31	-11.4	-24.9; 2.0	0.10	-10.6	-24.9; 3.7	0.15
AQLQ									
Symptoms									
ICS_{++} vs. $ICS_{+/-}$	-0.39	-0.68; -0.10	0.008	-0.33	-0.63; -0.03	0.03	-0.17	-0.50; 0.16	0.31
Activity limitation									
ICS_{++} vs. $ICS_{+/-}$	-0.48	-0.73; -0.24	0.0001	-0.32	-0.57; -0.07	0.01	-0.21	-0.47; 0.05	0.11
Emotional function									
ICS_{++} vs. $ICS_{+/-}$	-0.39	-0.68; -0.10	0.009	-0.37	-0.69; -0.05	0.02	-0.24	-0.57; 0.09	0.16
Environmental exposure									
ICS_{++} vs. $ICS_{+/-}$	-0.38	-0.68; -0.09	0.01	-0.52	-0.82; -0.21	0.001	-0.29	-0.62; 0.04	0.09
Overall AQLQ score									
ICS_{++} vs. $ICS_{+/-}$	-0.42	-0.67; -0.18	0.0008	-0.36	-0.62; -0.10	0.007	-0.21	-0.48; 0.06	0.13
Asthma control ‡									
ICS_{++} vs. $ICS_{+/-}$	3.50	1.80; 6.80	<0.0001	2.77	1.74; 4.41	<0.0001	2.48	1.10; 5.61	0.03

AQLQ, asthma quality of life questionnaire; FEV_1% predicted/year, Forced Expiratory Volume in 1 s % predicted measured at EGEA1 and 2, divided by the time of follow-up (i.e., a positive value represents a lung function decline); ICS, inhaled corticosteroids; $ICS_{+/-}$, subjects never or irregularly exposed to ICS (i.e., <6 months/year) between EGEA1 and 2; ICS_{++}, subjects regularly or continuously exposed to ICS (i.e., ≥6 months/year) between EGEA1 and 2.

* Linear regression analysis incorporating the modeled propensity score (including age, sex, occupational status, smoking status, age at asthma onset, severity of asthma, FEV_1% predicted [except for FEV_1 evolution], and skin prick tests) as the inverse probabilities of exposure weighting.

† Linear regression analysis with adjustment on variables included in the propensity score model (age, sex, occupational status, smoking status, age at asthma onset, severity of asthma, FEV_1% predicted [except for FEV_1 evolution], and skin prick tests).

‡ Odds ratio estimated from logistic regression analyses (partly-controlled/uncontrolled asthma vs. controlled).

Discussion

Applying the propensity score method, to better control the indication bias associated with this observational study, did not offer evidence of any long-term benefits of ICS on lung function decline, asthma control and HRQL in the 12-year follow-up EGEA study population.

The main strength of this study relates to the well-defined population. This longitudinal analysis included well-characterized subjects with persistent asthma, with detailed phenotypic data, recruited in the framework of the EGEA study. Each outcome was assessed by standardized and validated methods already used in international studies, reducing the measurement bias. Furthermore, a multiple imputation was performed to handle missing background data, and allow us to keep the whole population in the analysis.

Our study may suffer from potential limitations regarding the assessment of long-term ICS exposure. Inhaled corticosteroid exposure was assessed retrospectively by questionnaire over a long period, leading to potential misclassification bias. The treatment adherence and the inhaler technique, which are of concern for patients taking treatment for chronic conditions, were not assessed (161, 162). The clinical relevance of the 6 months/year ICS exposure threshold defined on the basis of the statistical distribution of the exposure in our population (similarly to de Marco et a1 (151)) has not been validated. The difference in the level of ICS exposure between the two groups may be insufficient. However, the sensitivity analysis comparing the extreme groups (i.e., subjects continuously vs. never exposed to ICS) led to the same conclusions, which may due to the small sample size or to the indication bias probably more important in this analysis.

Our results did not offer evidence of any long-term benefits of ICS on health-related outcomes but also suggest a trend for a small inverse association between asthma control, HRQL, and long-term ICS exposure. This finding likely reflects greater use of this therapy in

subjects with more severe post-baseline asthma. This may partly be explained by a remained indication bias after applying the propensity score method (i.e., subjects with severe asthma are more treated), because of the presence of unknown or inadequately measured confounders in the assessment of long-term benefits of ICS (145). For instance, asthma severity and socio-demographic characteristics, major determinants of ICS exposure, are difficult to assess accurately in such epidemiological survey. Further, by integrating only covariates measured at baseline and not time-varying factors, we were not able to capture the variability of the disease expression over time (i.e., asthma becoming more severe during the follow-up period), which may have biased our association estimates likely towards decreasing the potential benefits of long-term ICS use. Moreover, the assessment of the effects of long-term (11.5 years on average) ICS exposure on outcomes such as HRQL and asthma control referring to a much shorter period (i.e., last two weeks and three months, respectively) may be arguable. Indeed, to which extent the measure of such outcomes at a given time point efficiently reflects the long-term disease history is unclear. This may partly explain why a more important indication bias seems to remain for asthma control, and to a lower extent, for HRQL, as compared to the 11.5-year change in FEV_1, even after applying the propensity score method. We acknowledge that there may be a lack of time concordance between ICS use and the assessment of lung function evolution, but this may be difficult to improve in long-term follow-up. Though, as previously discussed by de Marco et al, the presence of lung function tracking and the regression toward the mean phenomenon are difficult to overcome with only two measurements over time (151). Finally, the definition of persistent asthma used was not specific and may lead to an underestimation of the associations because of the potential presence of subjects with intermittent asthma in the group never or irregularly exposed to ICS.

In accordance with the data from the literature, our results suggest a potential benefit of long-term ICS on lung function evolution in asthma (103, 104, 151). In two observational studies including 234 and 667 subjects with asthma followed during 10 and 9 years, the average FEV_1 decline was 18 (95%CI, 3.9-31.7; p = 0.01) and 11 (95%CI, 0.1-21; p = 0.02) mL/year slower in subjects exposed to ICS over a long period, compared with nonusers, respectively (104, 151). Interestingly, although not significant, the magnitude of the association was similar in our study. A statistical power of 80% was achieved for a difference of 17.4mL/year, which is equivalent to the difference evidenced in the study by Lange et al (104). On the basis of a cohort of 30,569 subjects with asthma from Saskatchewan Health databases, a nested case-control design found that the regular use of ICS was associated with reductions of 31% in the rate of hospital admissions with an early and stable effectiveness over time (148). These results suggest a benefit of ICS on some aspects of asthma control. However, a recent study based on a propensity score approach was unable to show any benefit of asthma maintenance therapy on the occurrence of acute exacerbation events among 4,275 children and young adults with asthma, using Medicaid claims files from 1997-1999 (145). Discrepancy between studies may relate to the phenotypic heterogeneity between populations. Because of the study design (subjects mainly recruited in chest clinics with current asthma), our population may include more subjects with moderate to severe asthma as compared with population-based studies, and therefore potentially more subjects with asthma resistant to corticosteroids.

A single propensity score model was performed to control the measured confounding for the health outcomes. Compared to outcome-specific model, this technique is preferred in terms of precision and bias of the effect estimates (163). The adequacy and the validity of the model was supported by a well goodness-of-fit, a non-significant Hosmer-Lemeshow test, and a c-index closed to 0.8, indicating a large degree of overlap in propensity scores between the

groups (130). Furthermore, even if its interpretation is subjective, the balance of covariates between never/regularly and irregularly/continuously exposed to ICS subjects within score's strata supported the usefulness of the propensity score model (133). In this analysis, the propensity scores were integrated as the IPTW, which tend to eliminate systematic differences between the two groups to a greater degree than stratification or covariate adjustment (164, 165). Moreover, IPTW method prevents the exclusion of subjects induced by the propensity score matching method (130).

Our study suggests that the propensity score method does not systematically better account for the indication bias associated with observational study than the conventional adjustment method. Less than 8-10 events per confounder were used for the propensity score modeling, allowing less biased, more robust and more precise estimates than multivariate models (166). Despite the theoretical benefits of the counterfactual methods as compared to the conventional regression models, some studies also reported comparable results between both approaches (145, 167, 168). It has been suggested that propensity score methods yield less biased estimates than multivariate model when the outcome is rare as it allows to account for more covariates in the model (125, 166).

In conclusion, it is one of the first attempts in the literature at the correction for the indication bias in the assessment of long-term asthma medication effects in an observational study. We believe our findings are of importance to help other investigators to design and conduct further pharmacoepidemiological analyses on the long-term effects of ICS in well-defined populations with detailed and prospective asthma treatment data.

Conflict of interest

Christophe Pison has received supports from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis to attend medical meeting and fees for conferences. Pierrick Bedouch has been reimbursed by GlaxoSmithKline and Novartis for international conference attendance. Jean Bousquet has received honoraria for participation in scientific and advisory boards, giving lectures, and press engagements from Actelion, Almirall, AstraZeneca, Chiesi, GlaxoSmithKline, Meda, Merck, Merck Sharpe & Dohme, Novartis, OM Pharma, Sanofi-Aventis, Schering Plough, Stallergènes, Takeda, Teva, and Uriach.

Ethics statement

Written consent was obtained from all participants at EGEA1 and 2. Ethical approval to carry out the study was granted for both surveys by the relevant committees (Cochin Royal Hospital, Paris, for EGEA1 and Necker-Enfants Malades Hospital, Paris, for EGEA2).

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Supplemental material

Methods

Population. EGEA is a French multicenter case-control and family-based study (Paris, Lyon, Marseille, Montpellier, and Grenoble). Indeed, 2,047 subjects aged 7 to 70 years were recruited at baseline (EGEA1; 1991-1995), including subjects with asthma recruited from chest clinics, their first-degree relatives and population-based controls. These subjects were invited to participate to the first follow-up of this study (EGEA2; 2003-2007) about 12 years later. Overall, the study included 904 subjects with ever asthma, for whom detailed individual and phenotypic characteristics were available. Examination at each survey (EGEA1 and 2) included a detailed questionnaire on asthma, based on standardized questions already used in international studies, a spirometry assessment to measure lung function, and a questionnaire on asthma treatments particularly detailed at EGEA2.

Asthma control. Asthma was defined as controlled if all the following features were present: no more than once per week of trouble breathing, no asthma attack in the last 3 months, no nocturnal symptom in the last 3 months, use of short-acting β_2-agonist inhalers less than 3 times per week in the last 3 months, no use of oral corticosteroids in the past year, and FEV_1 $\geq$80% predicted. If one or two of these features were absent, subjects were considered as partly controlled. Uncontrolled asthma was defined if subjects reported that three or more of these features were absent or if respiratory problems had caused hospital or emergency admissions in the past year or use of oral corticosteroids in the past year or more than 11 asthma attacks in the past 3 months.

Estimating propensity scores with incomplete data. The Missing At Random assumption was checked and a non-monotone missing pattern was observed for all covariates. A Markov Chain Monte Carlo method and a direct imputation method incorporated with the expectation-

maximization algorithm were used for quantitative and categorical covariates, respectively. The five simulations were averaged to test the adequacy of the propensity score model, and a sensitivity analysis was performed on each simulation to confirm the results.

Results

Table S1. Effects of the long-term inhaled corticosteroid exposure on lung function evolution, health-related quality of life, and asthma control among subjects continuously (n = 66) and never (n = 91) exposed between Epidemiological study in the Genetics and Environment of Asthma (EGEA) 1 and 2.

	Unadjusted model			Propensity score model †			Adjusted model ‡		
	β	95%CI	p value	β	95%CI	p value	β	95%CI	p value
FEV_1 evolution									
Change in FEV_1% predicted/year									
ICS_{+++} vs. ICS_{-}	-0.24	-0.64; 0.15	0.23	-0.24	-0.71; 0.22	0.31	-0.25	-0.75; 0.25	0.32
Change in FEV_1 (mL/year)									
ICS_{+++} vs. ICS_{-}	-4.4	-18.9; 10.0	0.55	-7.2	-23.9; 9.5	0.40	-7.8	-26.2; 10.6	0.41
AQLQ									
Symptoms									
ICS_{+++} vs. ICS_{-}	-0.59	-0.90; -0.29	0.0002	-0.62	-0.98; -0.27	0.0006	-0.46	-0.84; -0.07	0.02
Activity limitation									
ICS_{+++} vs. ICS_{-}	-0.59	-0.84; -0.34	<0.0001	-0.42	-0.70; -0.13	0.004	-0.36	-0.67; -0.05	0.02
Emotional function									
ICS_{+++} vs. ICS_{-}	-0.62	-0.93; -0.32	<0.0001	-0.62	-1.00; -0.24	0.001	-0.56	-0.95; -0.16	0.005
Environmental exposure									
ICS_{+++} vs. ICS_{-}	-0.43	-0.75; -0.10	0.01	-0.53	-0.90; -0.17	0.004	-0.36	-0.75; 0.04	0.08
Overall AQLQ score									
ICS_{+++} vs. ICS_{-}	-0.58	-0.83; -0.32	<0.0001	-0.54	-0.84; -0.24	0.0004	-0.43	-0.75; -0.11	0.008
Asthma control ǂ									
ICS_{+++} vs. ICS_{-}	5.17	2.44; 10.9	<0.0001	2.57	1.50; 4.41	0.0006	3.86	1.44; 10.37	0.007

AQLQ, asthma quality of life questionnaire; FEV_1% predicted/year, Forced Expiratory Volume in 1 s % predicted measured at EGEA1 and 2, divided by the time of follow-up (i.e., a positive value represents a lung function decline); ICS, inhaled corticosteroids; ICS_{-}, subjects never exposed to ICS between EGEA1 and 2; ICS_{+++}, subjects continuously exposed to ICS between EGEA1 and 2.

* Linear regression analysis incorporating the modeled propensity score (including age, sex, occupational status, smoking status, age at asthma onset, severity of asthma, FEV_1% predicted [except for FEV_1 evolution], and skin prick tests) as the inverse probabilities of exposure weighting.

† Linear regression analysis with adjustment on variables included in the propensity score model (age, sex, occupational status, smoking status, age at asthma onset, severity of asthma, FEV_1% predicted [except for FEV_1 evolution], and skin prick tests).

‡ Odds ratio estimated from logistic regression analyses (partly-controlled/uncontrolled asthma vs. controlled).

CHAPTER III

PHENOTYPES AND MEDICATIONS OF ASTHMA IN ELDERLY WOMEN: A LONGITUDINAL STUDY

Phenotypes and medications of asthma in elderly women: a longitudinal study

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Abstract

Rationale: With population ageing, further asthma research is needed in the elderly.

Objective: We assessed the relevance of the controller-to-total asthma medication ratio and its fluctuations over time to identify participants with a subsequent risk for poor asthma-related outcomes among well-characterized elderly women.

Methods: We studied 4,328 women with ever asthma (69.6 ± 6.1 years) from the Asthma-E3N study, which combined drug claims data since 2004 with prospective individual characteristics.

Measurements: The levels of the yearly controller-to-total asthma medication ratio were included in latent class analysis to identify groups of women characterized by specific long-term fluctuations of the ratio. Multiple regression models estimated the subsequent risk for uncontrolled asthma, asthma attacks, asthma exacerbations, and poor asthma-related quality of life associated with the level and the fluctuations of the ratio.

Main results: A ratio below 0.5 was significantly associated with a higher risk for subsequent uncontrolled asthma, asthma attacks and exacerbations (OR[CI95%] = 2.13 [1.41;3.23], 1.51 [1.01;2.26] and 2.18 [1.37;3.44], respectively), and a lower total asthma quality of life questionnaire score (β[CI95%] = -0.49 [-0.68;-0.29]). The analysis of the long-term fluctuations of the ratio identified five profiles ("Never regular treatment", 53.2%; "Persistent high ratio", 21.8%; "Increasing ratio", 4.4%; "Initiating treatment", 8.8%; "Treatment discontinuation", 11.8%). The subsequent risk for poor asthma-related outcomes was significantly higher in profiles characterized by no or interrupted asthma maintenance therapy over time, compared to the "Persistent high ratio" group.

Conclusions: The level and the long-term fluctuations of the controller-to-total asthma medication ratio predict poor asthma-related outcomes in elderly women.

Keywords: asthma; older age people; asthma phenotypes; asthma medications; drug claims data.

At a glance Commentary

Scientific Knowledge on the Subject

Age and gender differences exist in the control of asthma. A low controller-to-total asthma medication ratio, an indicator of poor asthma quality of care, increased the risk of uncontrolled asthma. However, no study addressed specifically the clinical relevance of this ratio in elderly women. In addition, no study characterized the long-term fluctuations of the ratio, which might capture asthma trajectories leading to uncontrolled asthma.

What This Study Adds to the Field

This is the first study investigating the long-term evolution of asthma therapeutic management over an eight-year period in elderly women. Our analysis relying on a large cohort shows that both the magnitude and the long-term fluctuations of the controller-to-total asthma medication ratio are able to identify subgroups of elderly women with asthma at increased risk for poor asthma-related outcomes. Our findings extend results from previous studies to support the relevance of this asthma quality of care indicator across all age range and showed the clinical relevance of the long-term trajectories of this ratio. We provided valuable insights into new ways to improve asthma quality of care at population level.

Introduction

According the World Health Organization, “Ageing well” is a global priority (169). The worldwide burden of ageing represents a public health challenge to adapt the quality of care of chronic diseases, such as asthma. Asthma in the elderly is a heterogeneous disease as prevalent as in the youngest population (5-10%) and affecting more often women (57-59, 64). Asthma in the elderly is marked by a poor control with a higher rate of mortality, healthcare

utilization, medical costs, and a poorer health-related quality of life (57, 59). Its management is hampered by multiple factors including misdiagnosis, underdiagnosis, undertreatment, and a potential lower drug response (3, 57-59, 64, 65). Current guidelines for asthma therapeutic management do not consider asthma in the elderly as a specific condition. In addition, older adults are usually not included in randomized controlled trials, limiting the extrapolation of the results to this age group (2, 58, 68).

The global burden of asthma needs ongoing monitoring aiming at identifying patients at high risk for poor health-related outcomes. Claims data provide the unique opportunity to prospectively follow large populations and identify such patients. Asthma medication ratios calculated from drug administrative data have been developed to assess the asthma quality of care (116-121). These ratios, mainly studied in the US population, have been shown to have a good predictive ability to detect adults with poor asthma-related outcomes in short term. However, such quality of care markers might behave differently in other countries with different healthcare system, or in an older population. Moreover, beside the level of this ratio estimated over a specific time-window, its long-term fluctuations have never been addressed. It is unknown to which extent these fluctuations over several years might identify specific asthma trajectories related to subsequent risk for poor asthma-related outcomes.

We prospectively investigated the controller-to-total asthma medication ratio in a unique population-based cohort of elderly women. Our specific aims were: 1) to characterize the controller-to-total asthma medication ratio in elderly women and to identify its determinants; 2) to prospectively assess the predictive ability of the level and the long-term fluctuations of the ratio for the subsequent risk of poor asthma-related outcomes.

Methods

Population

This analysis was performed among participants with ever asthma from the Asthma-E3N study. The Asthma-E3N study (2011-2012) is a nested case-control study on asthma within the E3N study (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale [MGEN]), a prospective study of major chronic diseases among female members of a French national health insurance plan covering mostly teachers, aged 40-65 years in 1990 (see Supplemental material, p. 103) (11, 143). All women who reported to have ever had asthma (i.e., defined by a positive answer to the single question "Have you ever had an asthma attack?") at least once between 1992 and 2008 (n = 7,100) and confirmed in the Asthma-E3N questionnaire were included in this analysis (11, 143, 170). In addition to detailed questionnaires, reimbursements for non-hospital medications were comprehensively collected from the MGEN database for each woman from 2004 onwards.

Level and long-term fluctuations of the controller-to-total asthma medication ratio

Asthma medications were identified by ATC (Anatomical Therapeutic Chemical) codes from the exhaustive MGEN drug database (171). As recently proposed, the controller-to-total asthma medication ratio was defined over 12 months as the ratio of the number of dispensed inhaled corticosteroids (ICS, alone and combined) and leukotriene receptor antagonists (LTRA) to the number of dispensed R03 medications (drugs for obstructive airway diseases according to the ATC classification) (121). As previously published, the ratio was calculated among women regularly exposed to asthma maintenance therapy (≥4 reimbursements of ICS or LTRA over 12 months) and a 0.5-threshold was used to define low (<0.5) vs. high ratio (≥0.5) (see Figure S1 in Supplemental material, p. 103) (116-121).

As previously used to define trajectories of wheezing phenotypes and specific IgE response, we applied latent class analysis, a data driven approach to identify groups of women characterized by the eight-year fluctuations of the ratio (see Supplemental material, p. 103) (172, 173).

Level of asthma therapy

The level of asthma therapy was determined over 12 months following the Global Initiative for Asthma (GINA) 2016 guidelines (see Supplemental material, p. 104) (2). Oral corticosteroids were not included in our classification because of their use for many other conditions than asthma, particularly in the elderly. The GINA treatment steps were gathered into two levels (steps 1, 2, and 3 vs. steps 4 and 5).

Asthma-related outcomes (see Supplemental material, p. 104)

Asthma control was assessed in the last month before the Asthma-E3N questionnaire by the standardized and validated Asthma Control Test (5). A 19-threshold was used to define controlled vs. uncontrolled asthma (5). The health-related quality of life was assessed by the standardized and validated Asthma Quality of Life Questionnaire (AQLQ) (157). The total AQLQ score was computed as the mean of all questions and was compared with the smallest difference considered clinically and socially relevant (0.5) (157). Asthma attack was assessed by a positive answer to “Have you had an asthma attack in the last 12 months?” in the Asthma-E3N questionnaire. Asthma exacerbation was defined as report of an asthma attack lasting at least two days during the same period. Severe exacerbation was defined with self-reported emergency health care utilization for asthma (emergency department visit or hospital admission), oral corticosteroid courses during at least three days or modification of asthma maintenance therapy (174).

Biases

A previous study showed that the women not invited to participate to the Asthma-E3N study (women who did not answered to the asthma question in the previous E3N questionnaires) did not show marked differences with Asthma-E3N participants (170).

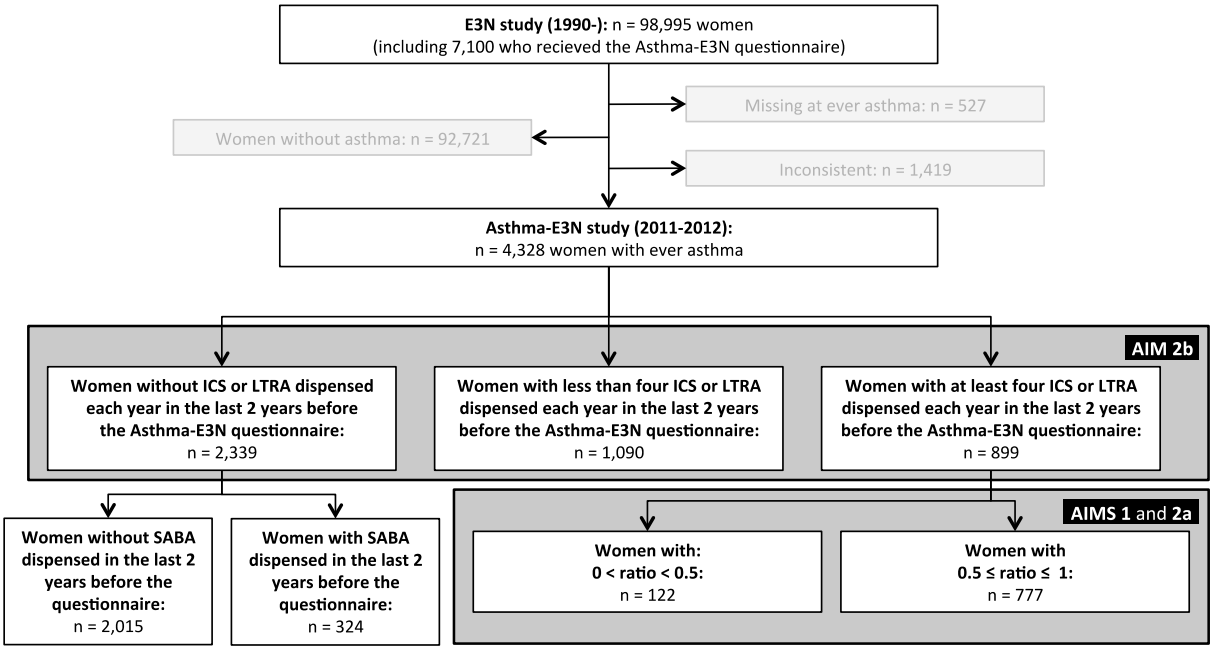
Statistical analysis (see Supplemental material, p. 105)

A multiple imputation (n = 20) was performed to avoid any population sample selection, leading to a loss of statistical power and potential bias related to not random selection (overall 10.3% of missing data). Linear and logistic regressions adjusted for age, active smoking, ever rhinitis and body mass index (BMI) were used to assess the predictive ability of the ratio for the subsequent risk of poor asthma-related outcomes. A sensitivity analysis considering a 0.75-threshold of the ratio according to the ratio distribution in our population was performed. We conducted two stratified analyses according to: 1) the level of asthma therapy, and 2) the chronic obstructive pulmonary disease (COPD) status.

Results

Study population

Among the 6,724 women who completed the Asthma-E3N questionnaire (response rate: 94.7%), 4,328 women reported to have ever had asthma (Figure 11). They were 69.6 ± 6.1 years old, mostly post graduated and non-currently smokers (Table VIII). Two thirds had late-onset asthma (≥40 years old) and 21.2% reported at least three symptoms in the last three months. Chronic obstructive pulmonary disease and ever rhinitis were reported by 22.7% and 72.1%, respectively.



E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonists; SABA, short acting $beta_2$-agonists.

Figure 11. Study population flowchart and study aims. "Inconsistent" defined women who did not report to have ever asthma in the Asthma-E3N questionnaire. AIM 1, to characterize the level of the controller-to-total asthma medication ratio in the elderly population and identify its determinants (n = 899); AIM 2, to prospectively assess the predictive ability of the level of the controller-to-total asthma medication ratio (n = 899) (2a) and its long-term fluctuations (n = 4,328) (2b) for the subsequent risk of poor asthma-related outcomes.

Among women regularly exposed to asthma maintenance therapy during the study period (n = 899), 13.6% had a low controller-to-total asthma medication ratio (<0.5). As compared to women with a higher ratio (≥0.5), women with a low ratio were older, less obese, more often ex- or current smokers, and had more often asthma symptoms, COPD, and reimbursements of asthma reliever medications (Table VIII and see Table S1 in Supplemental material, p. 106). Analyses adjusted for age showed similar results (data not shown).

Table VIII. Characteristics of the study population according to asthma medication reimbursements over the 24 months before the Asthma-E3N questionnaire.

Variable		Whole population (n = 4,328)		Women unexposed (n = 2,339)		Women irregularly exposed (n = 1,090)		Women regularly exposed						p value*	p value**
								Whole group (n = 899)		Ratio <0.5 (n = 122)		Ratio ≥0.5 (n = 777)			
Socio-demographic characteristics															
Age (years), mean ± SD		69.6	± 6.1	69.2	± 5.9	69.4	± 6.0	71.0	± 6.3	72.2	± 6.4	70.9	± 6.2	<0.0001	0.02
BMI (kg/m²), n (%)	<20	431	(10.9)	253	(11.9)	100	(10.1)	78	(9.5)	11	(9.8)	67	(9.4)	0.02	0.04
	20≤ BMI <25	2,082	(52.9)	1,159	(54.4)	492	(49.9)	431	(52.6)	56	(50.0)	375	(53.0)		
	25≤ BMI <30	1,035	(26.3)	526	(24.7)	283	(28.7)	226	(27.6)	25	(22.3)	201	(28.4)		
	≥30	389	(9.9)	193	(9.0)	111	(11.3)	85	(10.3)	20	(17.9)	65	(9.2)		
Education level, n (%)	<baccalaureate	449	(10.8)	251	(11.1)	109	(10.3)	89	(10.4)	14	(11.8)	75	(10.2)	0.0003	0.79
	Bac. – bac. +2	2,050	(49.2)	1,033	(45.8)	553	(52.6)	464	(54.2)	67	(56.3)	397	(53.9)		
	Bac. +3 – bac. + 4	840	(20.2)	487	(21.6)	204	(19.4)	149	(17.4)	20	(16.8)	129	(17.5)		
	≥bac. +5	826	(19.8)	486	(21.5)	186	(17.7)	154	(18.0)	18	(15.1)	136	(18.4)		
Smoking, n (%)	Never smoker	2,152	(50.1)	1,106	(47.6)	557	(51.8)	489	(54.6)	53	(43.8)	436	(56.3)	0.005	0.03
	Ex-smoker	1,975	(46.0)	1,118	(48.2)	482	(44.8)	375	(41.9)	62	(51.2)	313	(40.5)		
	Current smoker	166	(3.9)	98	(4.2)	37	(3.4)	31	(3.5)	6	(5.0)	25	(3.2)		
Comorbidities															
COPD, %		863	(22.7)	269	(13.0)	266	(28.0)	328	(41.6)	63	(57.8)	265	(39.0)	<0.0001	0.0002
Ever rhinitis, %		2,978	(72.1)	1,556	(69.8)	797	(76.3)	625	(72.9)	82	(68.9)	543	(73.6)	0.0004	0.29
Ever eczema, %		1,432	(34.4)	805	(35.8)	356	(33.9)	271	(31.4)	36	(30.8)	235	(31.5)	0.06	0.87
Asthma															
Age at asthma onset (years), %	Age <16	1,225	(30.9)	776	(36.4)	251	(25.4)	198	(23.5)	33	(28.9)	165	(22.7)	<0.0001	0.13
	16≤ age <40	1,282	(32.4)	717	(33.7)	318	(32.1)	247	(29.3)	37	(32.5)	210	(28.8)		
	Age ≥40	1,455	(36.7)	637	(29.9)	421	(42.5)	397	(47.2)	44	(38.6)	353	(48.5)		
Asthma symptoms, %	0	1,248	(37.5)	893	(47.5)	210	(26.6)	145	(21.9)	14	(16.9)	131	(22.7)	<0.0001	0.04
	1	891	(26.7)	582	(31.0)	168	(21.3)	141	(21.3)	13	(15.6)	128	(22.1)		
	2	488	(14.6)	189	(10.1)	157	(19.8)	142	(21.5)	15	(18.1)	127	(22.0)		
	≥3	705	(21.2)	217	(11.4)	255	(32.3)	233	(35.3)	41	(49.4)	192	(33.2)		
Parental asthma, %	None	3,071	(76.2)	1,714	(78.1)	748	(74.2)	609	(73.5)	80	(72.8)	529	(73.6)	0.02	0.53
	Father	454	(11.3)	239	(10.9)	108	(10.7)	107	(12.9)	11	(10.0)	96	(13.3)		
	Mother	437	(10.8)	208	(9.5)	131	(13.0)	98	(11.8)	16	(14.5)	82	(11.4)		
	Both	69	(1.7)	33	(1.5)	21	(2.1)	15	(1.8)	3	(2.7)	12	(1.7)		
Medical follow-up during the last 12 months, n (%)		1306	(33.1)	269	(12.3)	467	(48.5)	570	(72.2)	75	(73.5)	495	(72.0)	<0.0001	0.76
Regular monitoring for asthma		733	(18.3)	96	(4.3)	190	(19.4)	447	(55.0)	70	(60.3)	377	(54.2)	<0.0001	0.22
General practitioner		1188	(30.9)	304	(13.8)	437	(46.3)	447	(64.4)	67	(69.1)	380	(63.6)	<0.0001	0.30
Consultant		826	(21.7)	158	(7.3)	258	(28.3)	410	(56.3)	63	(64.3)	347	(55.1)	<0.0001	0.09

Bac, baccalaureate; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; SD, standard deviation.

* p value comparing the three groups of asthma maintenance therapy exposition (unexposed, irregularly and regularly exposed).

** p value comparing the two groups of the controller-to-total asthma medication ratio among women regularly exposed (ratio <0.5 and ratio ≥0.5).

Level of the controller-to-total asthma medication ratio and asthma-related outcomes

A low ratio was significantly associated with a higher risk for subsequent uncontrolled asthma, asthma attacks and exacerbations (adjusted ORs [CI95%] = 2.13 [1.41;3.23], 1.51 [1.01;2.26] and 2.18 [1.37;3.44], respectively), and a lower total AQLQ score (adjusted β [CI95%] = -0.49 [-0.68;-0.29], p <0.0001), as compared to those with a high ratio (Table IX and Figure 12a). Women with a low ratio had an increased risk for severe asthma exacerbation (adjusted OR [CI95%] = 2.08 [1.31;3.31]). Similar results were found in subjects with COPD except for asthma control for which no association was found (see Table S2 in Supplemental material, p. 107). Associations were unchanged when considering a ratio threshold of 0.75 (see Tables S3 and S4 in Supplemental material, p. 107).

Table IX. Description of the asthma-related outcomes according to the level of the controller-to-total asthma medication ratio (n = 899).

Outcome	Whole population		0≤ ratio <0.5		0.5≤ ratio ≤1		p value
Asthma control							
Controlled asthma, n (%)	477	(67.6)	48	(50.5)	429	(70.2)	0.0001
Uncontrolled asthma, n (%)	229	(32.4)	47	(49.5)	182	(29.8)	
Asthma symptoms							
At least one asthma attack, n (%)	336	(38.8)	54	(47.4)	282	(37.5)	0.04
At least one asthma exacerbation, n (%)	164	(21.1)	34	(33.3)	130	(19.2)	0.001
At least one severe exacerbation, n (%)	152	(19.7)	32	(31.7)	120	(17.9)	0.001
Leading to emergency visit or hospitalization at least one time, n (%)	26	(3.4)	6	(6.1)	20	(3.0)	0.12
Leading to oral corticosteroids at least 3 days at least one time, n (%)	143	(18.6)	30	(30.3)	113	(16.9)	0.001
Leading to asthma maintenance therapy modification, n (%)	77	(10.1)	18	(18.4)	59	(8.9)	0.004
Asthma related quality of life (AQLQ)							
Symptoms, m ± sd	5.6	± 1.1	5.2	± 1.2	5.6	± 1.1	<0.0001
Activity limitation, m ± sd	5.5	± 1.1	5.1	± 1.3	5.6	± 1.1	<0.0001
Emotional function, m ± sd	5.7	± 1.2	5.2	± 1.3	5.8	± 1.1	<0.0001
Environmental exposure, m ± sd	5.8	± 1.2	5.3	± 1.4	5.8	± 1.2	<0.0001
Overall score, m ± sd	5.6	± 1.0	5.1	± 1.2	5.7	± 1.0	<0.0001

m, mean; SD, standard deviation. Descriptive analysis was performed using not imputed data. Asthma control was defined using Asthma Control Test. Asthma-related quality of life was defined using the Asthma quality of life questionnaire.

Women with a low ratio had a significant lower asthma maintenance therapy level, as compared to those with a high ratio (22.2% vs. 5.1%, p = 0.0009) (see Figure S2 in Supplemental material, p. 108). The patterns of associations between the ratio and the asthma-related outcomes did not differ according to the level of asthma maintenance therapy (p interaction >0.41), although most of the associations did not reach the significance level in the

low asthma maintenance therapy group because of limited statistical power (Figures 12b and 12c).

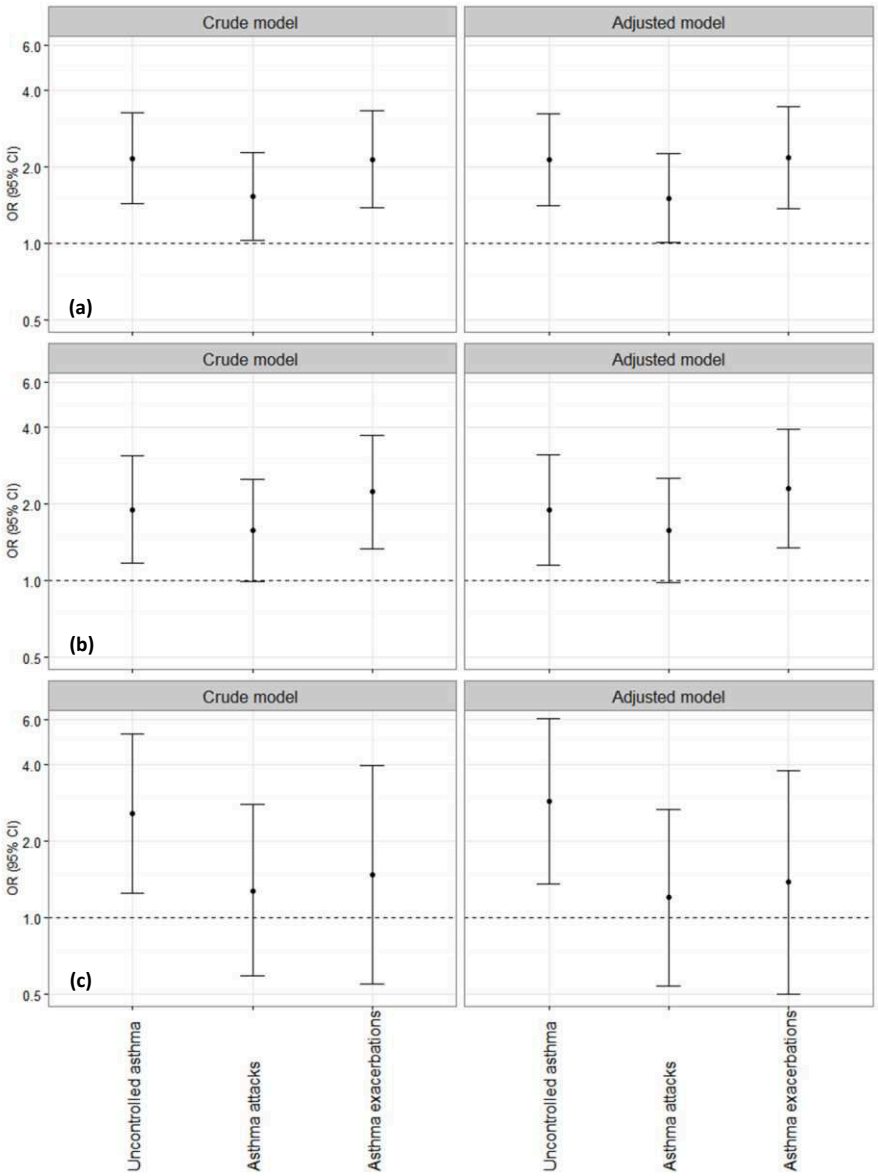


Figure 12. Predictive ability of the controller-to-total asthma medication ratio below 0.5 (odd ratio with confidence interval 95%) for poor asthma-related outcomes (uncontrolled asthma, asthma attacks and asthma exacerbations) among women regularly exposed to asthma maintenance therapy over the last 12 months (n = 899): (a) whole population, (b) women with a high asthma maintenance therapy level (steps 4 and 5 according to GINA classification; n = 555 over the two years preceding the Asthma-E3N questionnaire), and (c) women with a low asthma maintenance therapy level (steps 1 to 3 according to GINA classification; n = 344 over the two years preceding the Asthma-E3N questionnaire). Adjusted models included age, active smoking, ever rhinitis and body mass index.

Long-term fluctuations of the controller-to-total asthma medication ratio and asthma-related outcomes

Among the 4,328 women with ever asthma, the latent class analysis identified five groups of women characterized by their fluctuations of the ratio over the 2004-2011 period: (a) never regularly asthma maintenance therapy (<4 reimbursements of ICS and/LTRA during a year) (labeled "Never regular treatment"; n = 2,302; 53.2%), (b) persistent ratio ≥0.5 (labeled "Persistent high ratio"; n = 943; 21.8%), (c) increased ratio from <0.5 to ≥0.5 (labeled "Increasing ratio"; n = 190; 4.4%), (d) initiation of asthma maintenance therapy with a ratio ≥0.5 (labeled "Initiating treatment"; n = 381; 8.8%), and (e) cessation of asthma maintenance therapy during the period (labeled "Treatment discontinuation"; n = 512; 11.8%) (Figure 13). The mean posterior probability of belonging to the assigned cluster was 0.93 ± 0.13, indicating a clear delineation of the clusters.

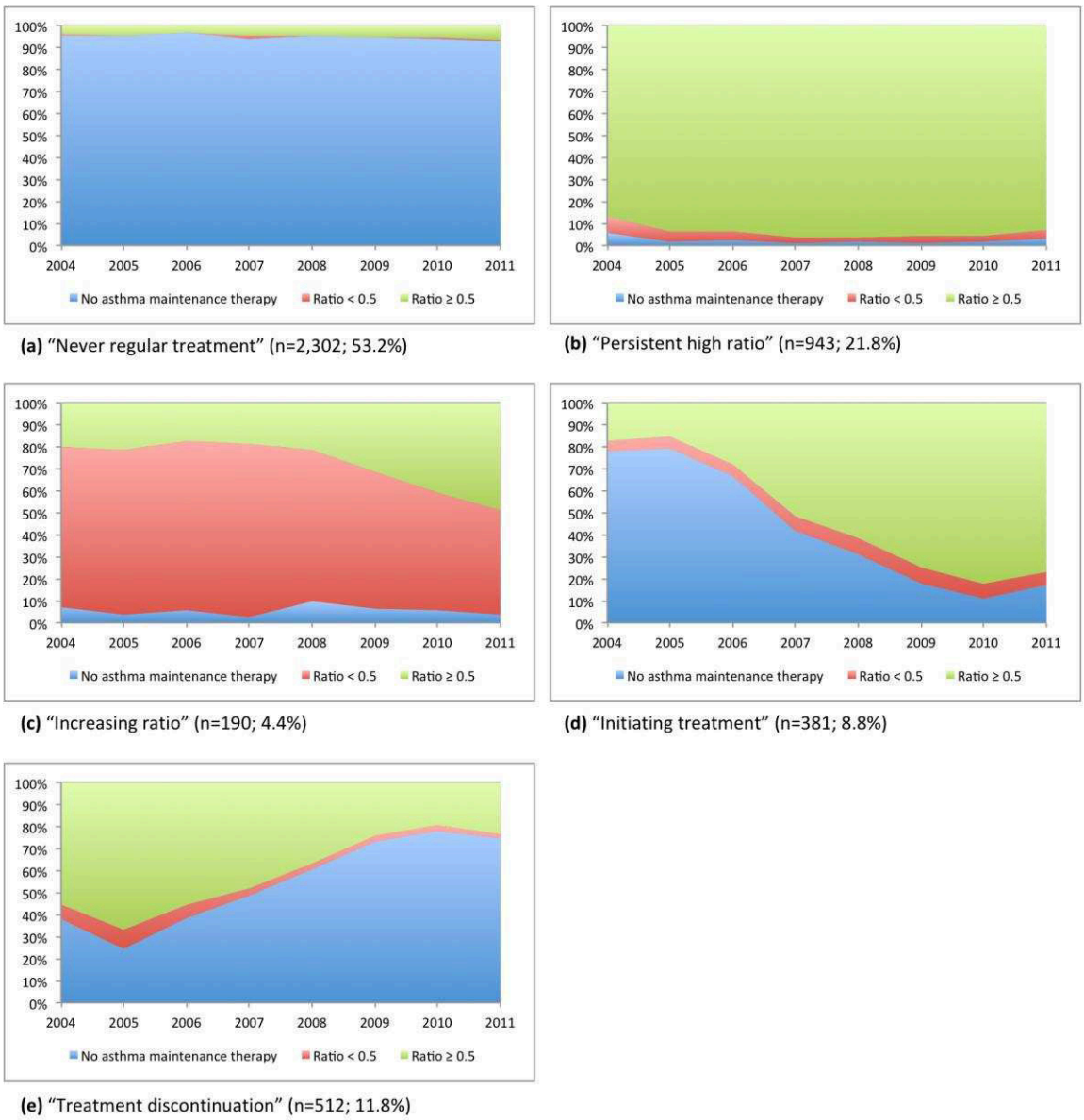


Figure 13. Description of the fluctuations of the controller-to-total asthma medication ratio over an eight-year period, defined by latent class analysis among women with ever asthma in the Asthma-E3N questionnaire (n = 4,328): (a) never regularly asthma maintenance therapy (labeled "Never regular treatment"), (b) persistent controller-to-total asthma medication ratio ≥0.5 (labeled "Persistent high ratio"), (c) increased controller-to-total asthma medication ratio from <0.5 to ≥0.5 (labeled "Increasing ratio"), (d) initiation of asthma maintenance therapy with a controller-to-total asthma medication ratio ≥0.5 (labeled "Initiating treatment"), and (e) cessation of asthma maintenance therapy during the period (labeled "Treatment discontinuation").

Women belonging to the “Persistent high ratio” cluster were less often ever smokers than those in the other clusters (see Table S5 in Supplemental material, p. 109). As compared to women from the cluster “Persistent high ratio”, women from the clusters “Never regular treatment”, “Initiating treatment”, and “Treatment discontinuation” had a younger age, a higher education level, and reported less often COPD and medical follow-up. As compared to the reference group (“Persistent high ratio”), women belonging to the “Increasing ratio”, “Initiating treatment”, and “Treatment discontinuation” clusters had a higher BMI and those belonging to the “Never regular treatment” cluster had less asthma symptoms, rhinitis, and a younger age of asthma onset.

Women belonging to the “Never regular treatment” and “Treatment discontinuation” clusters had a significant increased risk for subsequent uncontrolled asthma and asthma attacks/exacerbations, as compared to those belonging to the reference group (Figure 14). Inversely, the “Increasing ratio” and “Initiating treatment” clusters were associated with a significant lower risk for subsequent uncontrolled asthma and asthma attacks/exacerbations.

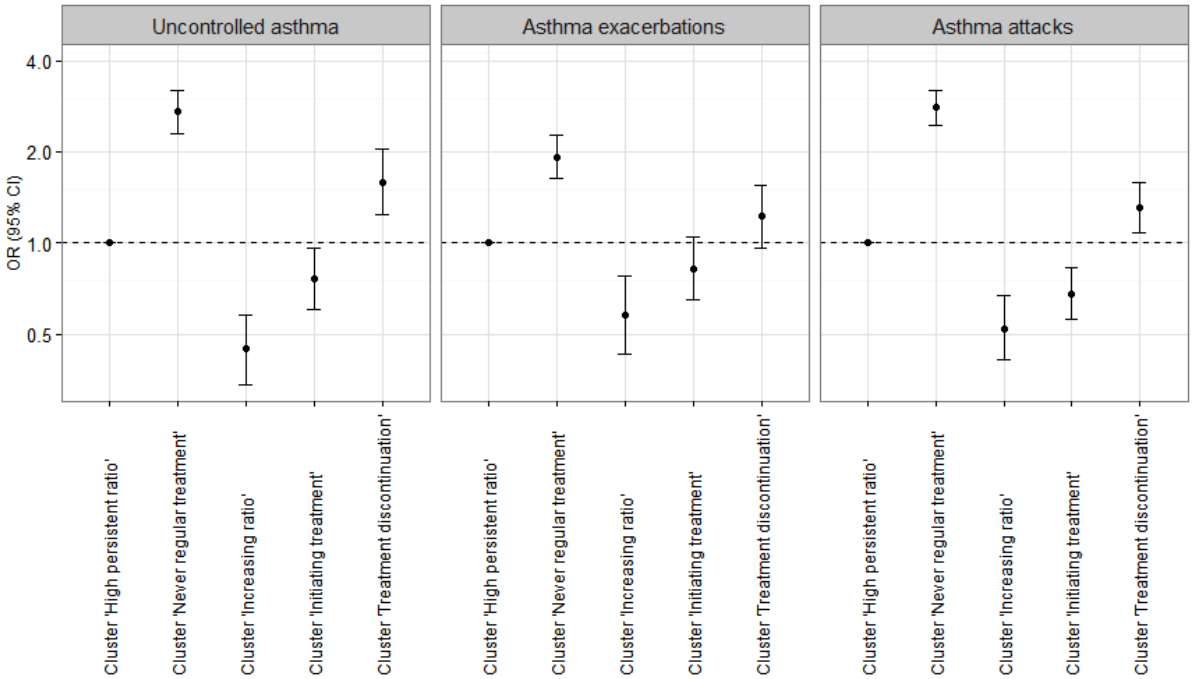


Figure 14. Associations (odd ratio with confidence interval 95%) between the clusters of the fluctuations of the controller-to-total medication ratio obtained by latent class analysis and poor asthma-related outcomes (uncontrolled asthma, asthma attacks and asthma exacerbations) among women with ever asthma in the Asthma-E3N study (n = 4,328). Logistic regressions were weighted by the probability to belong to the cluster.

Discussion

This is the first study showing that a low level of the controller-to-total asthma medication ratio increases the subsequent risk for poor asthma-related outcomes in elderly women. By investigating a new feature of this ratio, its long-term fluctuations, we identify specific asthma trajectories at increased risk for poor asthma-related outcomes.

A novelty of our analysis relies on the focus in an elderly population (58). Asthma therapeutic management in the elderly represents a major challenge because of the lack of specific guidelines for this population which is increasing (2, 57). A major strength of our study relies on the design of the Asthma-E3N study, combining personal and phenotypic

characteristics collected by questionnaire complemented by an independent eight-year comprehensive drug database from 2004. The study design allowed to include all participants with ever asthma in a drug database study, independently of the asthma treatment status, limiting the selection bias. The Asthma-E3N study allows a comprehensive assessment of different domains of asthma-related outcomes derived from standardized and validated questionnaires or very specific validated asthma-related questions. The detailed questionnaires enabled us to take into account confounders in the estimated associations, which is an improvement as compared with most of the previous studies related to the asthma medication ratio. We acknowledge that our study has some limitations. The Asthma-E3N study included only women limiting the external validity to men. Nevertheless, our findings are highly relevant from the public health viewpoint because asthma in elderly women is more prevalent and severe than in men (64). Ever asthma was defined by a positive answer to the question "Have you ever had an asthma attack?", a question widely used in epidemiological studies according to the American Thoracic Society Epidemiology Standardization Project (9). As previously shown in the E3N population, the repeated answer to this question over time improved the assessment of ever asthma, limiting potential misdiagnosis (170). Moreover, the associations between the ratio and asthma-related outcomes were estimated in women regularly exposed to asthma maintenance therapy (≥4 reimbursements of ICS or LTRA in the past 12 months), for which the diagnosis of asthma is very likely. To define the asthma-COPD overlap syndrome (ACOS), COPD was assessed by questionnaire, as the protocol did not include lung function measurements (3, 58, 59, 64). However, the self-report of COPD was validated in a previous study among health professionals (175).

The controller-to-total asthma medication ratio included LTRA in the numerator, as suggested in a recent study (121). Considering LTRA in the ratio is relevant in the elderly

because it has been suggested LTRA improve asthma control in this population (59, 176). The two-class ratio we used is easily applicable in practice but it does not include the number of doses per unit or the potency of ICS drugs. Weighted ratios including these features have been proposed but displayed similar performance (177). Our findings show that both 0.5 and 0.75-thresholds for the controller-to-total asthma medication ratio performed similarly when studied in relation with asthma-related outcomes in elderly women. Our study combined with previous studies supports the 0.5-threshold of this unweighted ratio (120, 121, 177).

Our findings extend those from previous studies by showing that the controller-to-total asthma medication ratio, using administrative data as quality-of-care marker, is also relevant in older age people (116-121). The low prevalence of reported emergency department visit/hospitalization for asthma in the preceding 12 months before the Asthma-E3N questionnaire reported in this study (2.8%) did not enable us to properly address the association between the ratio and this outcome in our elderly population (116, 117, 120, 121). Nevertheless, analyses considering severe exacerbations showed similar patterns of association as those observed for any exacerbations. Interestingly, although the statistical power of the stratified analyses was limited and prevent any firm conclusion, our findings suggest the relevance of the ratio whatever the asthma severity, but the ratio might be less relevant in ACOS, a specific phenotype. Overall, our study suggests that the controller-to-total asthma medication ratio is a clinically relevant marker in asthma across the whole age range, regardless of asthma severity, but might be of lesser interest in ACOS.

For the first time, we characterized the long-term fluctuations of the controller-to-total asthma medication ratio and showed that some specific longitudinal profiles were associated with the subsequent risk for poor asthma-related outcomes. Asthma follows a dynamic process with variation of the disease manifestation over time (178, 179). Compared to most chronic diseases, asthma does not always get worse with time and little is known about its

long-term fluctuations (179). Previous studies have shown that the short-term fluctuations of airway function among subjects with asthma were related to the risk for subsequent poor asthma-related outcomes (178, 180). Recently, using a similar data-driven approach on administrative linked health records, three trajectories of childhood asthma phenotypes were distinguished and differentially associated with environmental exposures (181). Here, we identified five long-term trajectories of the ratio over eight years. The risk for subsequent poor asthma-related outcomes significantly differed between the clusters, higher risk being observed in subjects un- or interrupted exposed to asthma maintenance therapy over time, as compared to those in the "Persistent high ratio" cluster. Our findings highlight the importance of characterizing the variability in asthma quality of care over time and suggest a new approach to analyze asthma treatments in the context of drug administrative database surveillance.

In conclusion, our findings, that identified markers from drug claims data able to target elderly people at increased risk for poor asthma control, are particularly relevant in the context of the policies on ageing, where health and care services are undergoing changes to adapt systems to the growing demands caused by expansion of chronic diseases and ageing. The information obtained from this study will be valuable in the frame of the initiative AIRWAYS ICPs (Integrative care pathways for airway diseases), approved by the European Innovation Partnership on Active and Healthy Ageing, aiming to launch a collaboration to develop practical multisectoral care pathways to reduce chronic respiratory disease burden, mortality and multimorbidity (41). In the context of pharmacoepidemiological surveillance by drug administrative databases, we provided valuable insights into new ways to improve asthma quality of care.

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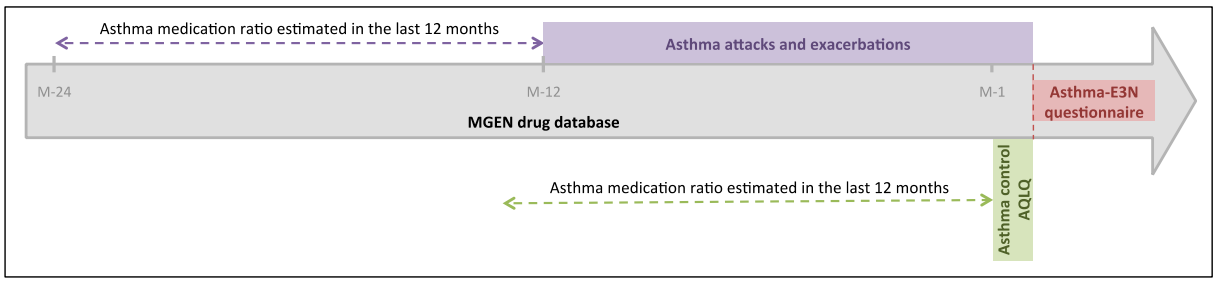
Supplemental material

Methods

Population. The study protocol was approved by the French Institutional Ethics Committee and written informed consent was obtained for all participants. Ethical approval was granted to use the MGEN database.

Level and long-term fluctuations of controller-to-total asthma medication ratio



AQLQ, Asthma Quality of Life Questionnaire; M, month

Figure S1. Study design for the definition of the level of the controller-to-total asthma medication ratio. The level of the controller-to-total asthma medication ratio was estimated from the MGEN drug database in the last 12 months before each health-related outcome (asthma control, asthma attacks, asthma exacerbations, and health-related quality of life).

The levels of the yearly controller-to-total asthma medication ratio were included in latent class analysis (LCA), a data driven approach, to identify groups of women characterized by the eight-year fluctuations of the ratio (2004-2011), as previously used to identify longitudinal wheezing phenotypes or specific IgE patterns (172, 173). LCA is a cluster-based model, used here to identify subgroups of subjects sharing a similar history in their asthma medication therapies. LCA estimates two sets of parameters: i) the conditional probabilities, which represent the probabilities of belonging to a class given a specific pattern of the ratio, and ii) the posterior probabilities of cluster membership for each woman given their history of the

asthma medication ratio (derived from the conditional probabilities). The number of profiles was determined using both the Akaike information criterion and Bayesian information criterion (182). Compared with traditional classification approaches, the main advantages of LCA are based on: 1) the presence of model selection criteria in order to define the number of classes, 2) the absence of a priori choice of a distance measurement, and 3) the probabilistic approach for determining the probability of belonging to each class for each women (information about the "uncertainty" of the classification).

The impact of the longitudinal profiles of the ratio derived from the LCA for the subsequent risk of uncontrolled asthma, asthma attacks and exacerbations was estimated by logistic regressions weighted by the posterior probability of belonging to the cluster to account for the uncertainty in the cluster membership. The latent class analyses were performed using the SAS 9.4 statistical software (SAS Institute, Cary, NC). The SAS LCA procedure was used (available at: http://methodology.psu.edu/).

Level of asthma therapy. The level of asthma therapy was defined following the GINA 2016 guidelines (2): 1) Step 1, regular use of inhaled corticosteroids (ICS) or leukotriene receptor antagonists (LTRA) over the 12 months (≥4 reimbursements during the period) but not enough to be defined as daily asthma maintenance therapy, 2) Step 2, low daily dose of ICS or LTRA or xanthines alone, 3) Step 3, either a) low daily dose of ICS associated with long-acting beta$_2$-agonists or LTRA or theophylline or b) medium/high daily dose of ICS, 4) Step 4, medium/high daily dose of ICS associated with long-acting beta$_2$-agonists or high daily dose of ICS associated with LTRA or theophylline, 5) Step 5, add-on treatment (e.g., omalizumab) except for oral corticosteroids.

Asthma-related outcomes. Asthma control was assessed in the last month before the Asthma-E3N questionnaire by the Asthma Control Test. It covers five domains (symptom frequency,

rescue therapy utilization, sleep interference, activity limitation, and self-rating of control) and varies from 5 to 25 (i.e., higher score meaning better asthma control) (5). We used a 19-threshold to define controlled vs. uncontrolled asthma (5). The health-related quality of life was assessed by the Asthma Quality of Life Questionnaire (AQLQ), consisting of 32 questions relating to the past two weeks before the Asthma-E3N questionnaire, and covering four domains (symptoms, activity limitation, emotional function and susceptibility to environmental exposure) (157). The total AQLQ score was computed as the mean of all questions and was compared with the smallest difference considered clinically and socially relevant (0.5) (157).

Statistical analysis. Socio-demographic characteristics included age, body mass index (BMI), education level (defined by the number of year post baccalaureate: <0, 0 to 2, 3 to 4, and ≥5), and active smoking (never, ex- and current smoker). Asthma characteristics included age at asthma onset (<16, 16 to 40, and ≥40 years old), a three-class asthma symptom score according to GINA recommendations assessed over the last three months before the Asthma-E3N questionnaire, and parental history of asthma (none, father, mother and both). Chronic comorbidities strongly associated with asthma (ever eczema, ever rhinitis, chronic obstructive pulmonary disease) were also included. Medical follow-up (frequency of medical consultations and physician specialization) was assessed in the past 12 months before the Asthma-E3N questionnaire.

Results

Table S1. Description of asthma medication treatments among the study population according to asthma medication reimbursements over the 24 months before the Asthma-E3N questionnaire.

Mean number of reimbursed units per 12-month period (mean ± sd)	Whole population (n = 4,328)	Women unexposed (n = 2,339)	Women irregularly exposed (n = 1,090)	Women regularly exposed			p value*	p value**
				Whole group (n = 899)	Ratio <0.5 (n = 122)	Ratio ≥0.5 (n = 777)		
Controller medications								
Inhaled corticosteroids (any type)	2.05 ± 3.51	0	1.69 ± 1.37	7.83 ± 3.56	8.21 ± 3.36	7.77 ± 3.59	<0.0001	0.20
Inhaled corticosteroids (alone)	0.62 ± 1.89	0	0.66 ± 1.00	2.17 ± 3.55	5.16 ± 4.20	1.69 ± 3.19	<0.0001	<0.0001
Inhaled corticosteroids (ICS-LABA fixed combination)	1.44 ± 3.00	0	1.03 ± 1.33	5.66 ± 4.21	3.05 ± 4.11	6.08 ± 4.07	<0.0001	<0.0001
Leukotriene receptor antagonists	0.72 ± 2.62	0	0.22 ± 0.77	3.18 ± 4.95	0.86 ± 2.70	3.55 ± 5.13	<0.0001	<0.001
Long-acting beta$_2$-agonists (other than ICS-LABA fixed combination)	0.39 ± 1.79	0.04 ± 0.50	0.42 ± 1.74	1.27 ± 3.17	5.28 ± 4.90	0.64 ± 2.22	<0.0001	<0.0001
Cromones	0.001 ± 0.023	0	0.002 ± 0.034	0.002 ± 0.033	0	0.003 ± 0.036	0.005	0.43
Xanthines	0.07 ± 0.93	0.01 ± 0.39	0.07 ± 0.97	0.24 ± 1.61	1.32 ± 3.72	0.07 ± 0.80	<0.0001	<0.0001
Omalizumab	0.01 ± 0.40	0	0	0.06 ± 0.88	0.18 ± 1.43	0.05 ± 0.76	0.0001	0.12
Long-acting muscarinic antagonists	0.20 ± 1.29	0.03 ± 0.44	0.15 ± 0.88	0.73 ± 2.50	3.12 ± 4.72	0.36 ± 1.64	<0.0001	<0.0001
Reliever medications								
Short-acting beta$_2$-agonists	0.58 ± 1.40	0.14 ± 0.51	0.77 ± 1.38	1.52 ± 2.24	2.89 ± 3.46	1.31 ± 1.90	<0.0001	<0.0001
Short-acting muscarinic antagonists	0.05 ± 0.51	0.004 ± 0.066	0.05 ± 0.45	0.17 ± 0.99	0.70 ± 2.22	0.08 ± 0.57	<0.0001	<0.0001

ICS, inhaled corticosteroids; LABA, long-acting beta$_2$-agonists.

* p value comparing the three groups of asthma maintenance therapy exposition (unexposed, irregularly and regularly exposed).

** p value comparing the two groups of controller-to-total asthma medication ratio among women regularly exposed (ratio <0.5 and ratio ≥0.5).

Table S2. Stratified analysis on chronic obstructive pulmonary disease (COPD) for the predictive ability of the controller-to-total asthma medication ratio below 0.5 (odd ratio or *beta with confidence interval 95%) for poor asthma-related outcomes (uncontrolled asthma, asthma attacks and exacerbations, and poor asthma-related quality of life) in women with asthma maintenance therapy over the last 12 months of each health outcome. Models were adjusted for age, active smoking, ever rhinitis and body mass index.

Outcome	Women with COPD (n = 328)			Women without COPD (n = 460)		
	OR	[CI95%]	p	OR	[CI95%]	p value
Uncontrolled asthma						
Ratio <0.5 vs. ratio ≥0.5	1.32	[0.74;2.35]	0.34	3.83	[1.93;7.63]	0.0001
Asthma exacerbations						
Ratio <0.5 vs. ratio ≥0.5	2.01	[1.08;3.76]	0.03	2.30	[1.11;4.80]	0.03
Asthma attacks						
Ratio <0.5 vs. ratio ≥0.5	1.61	[0.90;2.85]	0.11	1.64	[0.87;3.07]	0.12
Asthma related quality of life (AQLQ)*						
Ratio <0.5 vs. ratio ≥0.5	-0.37	[-0.66;-0.07]	0.01	-0.55	[-0.86;-0.25]	0.0003

Table S3. Description of the asthma-related outcomes according to a 0.75-threshold of the controller-to-total asthma medication ratio (n = 899).

Outcome	Whole population		0 ≤ ratio < 0.75		0.75 ≤ ratio ≤ 1		p value
Asthma control							
Controlled, n (%)	477	(67.6)	136	(52.9)	341	(76.0)	<0.001
Uncontrolled, n (%)	229	(32.4)	121	(47.1)	108	(24.0)	
Asthma Symptoms							
At least 1 asthma attack, n (%)	336	(38.8)	132	(42.7)	204	(36.6)	0.08
At least 1 asthma exacerbation, n (%)	164	(21.1)	78	(28.6)	86	(17.0)	0.0002
Asthma related quality of life (AQLQ)							
Symptoms, m ± SD	5.6	± 1.1	5.3	± 1.2	5.8	± 1.1	<0.0001
Activity limitation, m ± SD	5.5	± 1.1	5.2	± 1.2	5.7	± 1.0	<0.0001
Emotional function, m ± SD	5.7	± 1.2	5.4	± 1.3	5.9	± 1.1	<0.0001
Environmental exposure, m ± SD	5.7	± 1.2	5.4	± 1.3	5.9	± 1.2	<0.0001
Overall score, m ± SD	5.6	± 1.0	5.3	± 1.1	5.8	± 1.0	<0.0001

M, mean; SD, standard deviation. Descriptive analysis was performed using not imputed data. Asthma control was defined using Asthma Control Test. Asthma-related quality of life was defined using the Asthma quality of life questionnaire.

Table S4. Predictive ability of the controller-to-total asthma medication ratio below 0.75 (odd ratio or *beta with confidence interval 95%) for poor asthma-related outcomes (uncontrolled asthma, asthma attacks and exacerbations, and poor asthma-related quality of life) in women with asthma maintenance therapy over the last 12 months of each health outcome (n = 899). Adjusted models included age, active smoking, ever rhinitis and body mass index.

Outcome	Crude model			Adjusted model		
	OR	[CI95%]	p	OR	[CI95%]	p value
Uncontrolled asthma						
Ratio <0.75 vs. ratio ≥0.75	2.85	[2.09;3.90]	<0.0001	2.79	[2.03;3.84]	<0.0001
Asthma exacerbations						
Ratio <0.75 vs. ratio ≥0.75	1.98	[1.42;2.76]	<0.0001	2.08	[1.48;2.92]	<0.0001
Asthma attacks						
Ratio <0.75 vs. ratio ≥0.75	1.28	[0.97;1.70]	0.08	1.31	[0.98;1.74]	0.07
Asthma related quality of life (AQLQ)*						
Ratio <0.75 vs. ratio ≥0.75	-0.50	[-0.65;-0.36]	<0.0001	-0.48	[-0.61;-0.34]	<0.0001

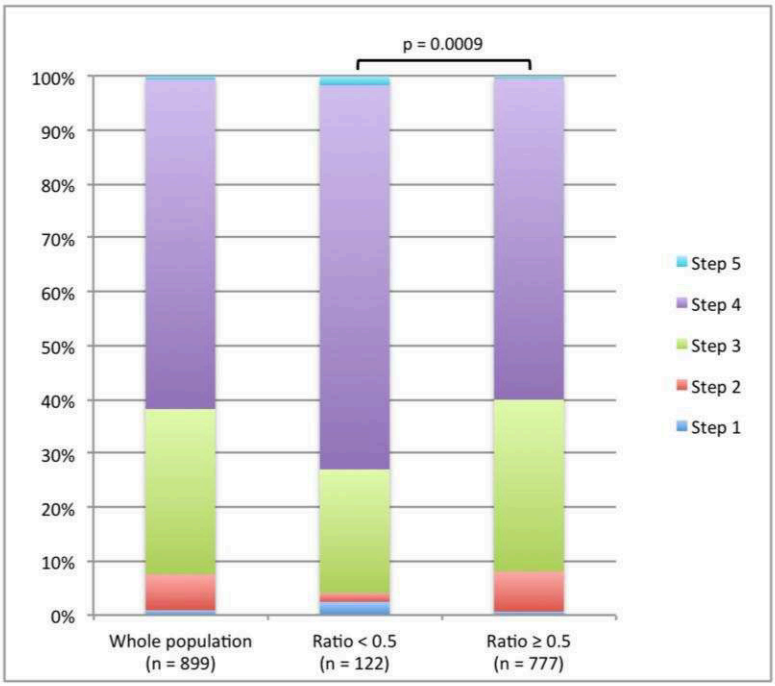


Figure S2. Distribution of GINA 2016 levels of asthma therapy management according to the level of the controller-to-total asthma medication ratio.

Table S5. Characteristics of the five trajectories of the controller-to-total asthma medication ratio identified by latent class analysis over an eight-year period among women with ever asthma in the Asthma-E3N study.

Variable		Whole population (n = 4,328)		Never regular treatment (n = 2,302)		Persistent high ratio (n = 943)		Increasing ratio (n = 190)		Initiating treatment (n = 381)		Treatment discontinuation (n = 512)		p value
Socio-demographic characteristics														
Age (years), mean ± SD		69.6	± 6.1	69.2	± 5.9	70.6	± 6.2	71.4	± 6.4	69.9	± 6.2	69.0	± 6.0	<0.0001
BMI (kg/m²), n (%)	<20	431	(10.9)	246	(11.7)	89	(10.3)	18	(10.3)	30	(8.7)	48	(10.5)	<0.0001
	20≤ BMI <25	2,082	(52.9)	1,168	(55.6)	466	(54.1)	85	(48.6)	158	(45.5)	205	(45.1)	
	25≤ BMI <30	1,035	(26.3)	518	(24.7)	226	(26.3)	49	(28.0)	108	(31.1)	134	(29.5)	
	≥30	389	(9.9)	167	(8.0)	80	(9.3)	23	(13.1)	51	(14.7)	68	(14.9)	
Education level, n (%)	<baccaleureate	449	(10.8)	245	(11.0)	79	(8.8)	17	(9.1)	43	(11.6)	65	(13.2)	<0.0001
	Bac. – bac. +2	2,050	(49.2)	1,038	(46.8)	484	(53.8)	105	(56.2)	215	(58.3)	208	(42.4)	
	Bac. +3 – bac. + 4	840	(20.2)	479	(21.6)	169	(18.8)	35	(18.7)	53	(14.4)	104	(21.2)	
	≥bac. +5	826	(19.8)	457	(20.6)	167	(18.6)	30	(16.0)	58	(15.7)	114	(23.2)	
Smoking, n (%)	Never smoker	2,152	(50.1)	1,076	(47.0)	536	(57.3)	95	(50.8)	191	(50.4)	254	(50.3)	0.0001
	Ex-smoker	1,975	(46.0)	1,113	(48.7)	371	(39.7)	81	(43.3)	175	(46.2)	235	(46.5)	
	Current smoker	166	(3.9)	98	(4.3)	28	(3.0)	11	(5.9)	13	(3.4)	16	(3.2)	
Comorbidities														
COPD, %		863	(22.7)	263	(12.9)	320	(38.2)	79	(47.0)	103	(32.3)	98	(22.1)	<0.0001
Ever rhinitis, %		2,978	(72.1)	1,536	(69.9)	667	(74.4)	139	(76.0)	271	(74.5)	365	(74.8)	0.02
Ever eczema, %		1,432	(34.4)	797	(36.0)	285	(31.6)	52	(28.7)	131	(35.3)	167	(34.1)	0.08
Asthma														
Age at asthma onset (years), %	Age <16	1,225	(30.9)	783	(37.4)	192	(21.8)	53	(29.9)	77	(22.4)	120	(25.7)	<0.0001
	16≤ age <40	1,282	(32.4)	724	(34.6)	263	(29.8)	66	(37.3)	99	(28.8)	130	(27.9)	
	Age ≥40	1,455	(36.7)	587	(28.0)	426	(48.4)	58	(32.8)	168	(48.8)	216	(46.4)	
Asthma symptoms, %	0	1,248	(37.5)	880	(48.2)	166	(23.8)	18	(12.5)	50	(19.1)	134	(33.4)	<0.0001
	1	891	(26.7)	548	(30.0)	150	(21.5)	26	(18.1)	58	(22.1)	109	(27.1)	
	2	488	(14.6)	186	(10.2)	150	(21.5)	27	(18.7)	63	(24.1)	62	(15.4)	
	≥3	705	(21.2)	212	(11.6)	232	(33.2)	73	(50.7)	91	(34.7)	97	(24.1)	
Parental asthma, %	None	3,071	(76.2)	1,676	(78.0)	636	(72.9)	127	(74.7)	272	(75.3)	360	(75.2)	0.09
	Father	454	(11.3)	235	(11.0)	108	(12.4)	18	(10.6)	43	(11.9)	50	(10.4)	
	Mother	437	(10.8)	205	(9.5)	116	(13.3)	20	(11.8)	36	(10.0)	60	(12.5)	
	Both	69	(1.7)	33	(1.5)	12	(1.4)	5	(2.9)	10	(2.8)	9	(1.9)	
Medical follow-up during the last 12 months, n (%)		1,306	(33.1)	282	(13.2)	561	(67.4)	119	(73.0)	194	(57.6)	150	(31.9)	<0.0001
Regular monitoring for asthma		733	(18.3)	88	(4.1)	415	(48.7)	96	(55.8)	86	(25.6)	48	(10.0)	<0.0001
General practitioner		1,188	(30.9)	318	(14.7)	439	(59.7)	110	(69.2)	172	(53.9)	149	(31.9)	<0.0001
Consultant		826	(21.7)	166	(7.8)	379	(49.5)	82	(54.0)	116	(37.4)	83	(18.2)	<0.0001

Bac, baccalaureate; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; SD, standard deviation

CHAPTER IV

IMPACT OF "PHARMACOME" ON ASTHMA CHARACTERISTICS

Impact of "Pharmacome" on asthma characteristics

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Abstract

Background: Polymedication related to comorbidities are common in asthma, particularly in the elderly. We aimed to comprehensively characterize the drugs used in elderly women with asthma and assess associations between polymedication and asthma characteristics.

Methods: We performed a network-based analysis on drug administrative databases to visualize the prevalence of drug classes and their associations among old women from the Asthma-E3N study ("Pharmacome"). A clustering method relying on medications was performed to identify asthma groups sharing similar medication profiles. Regression models estimated the associations between medication profiles and asthma characteristics (uncontrolled asthma, asthma attack/exacerbation, asthma severity, late-onset asthma, health-related quality of life, and asthma-chronic obstructive pulmonary disease overlap syndrome).

Results: Among the 4,328 women with ever asthma, 4,078 (94.2%) used other medications than for asthma. The "Pharmacome" identified 177 drug classes and 282 links between drug classes, including 31 links with asthma medications. Latent class analysis restricted to drug classes associated with asthma identified three medication profiles: "Few comorbidity-related medications" (50.1%), "Predominant allergy-related medications" (27.0%), and "Predominant cardiovascular-related medications" (22.9%). Compared to subjects belonging to the "Few comorbidity-related medications" cluster, subjects belonging to the two other clusters had significantly more often uncontrolled asthma, asthma attacks and exacerbations, a higher level of asthma treatment, a later asthma-onset and a poorer health-related quality of life.

Conclusion: Our integrative approach relying on drug administrative database provides valuable insights to decipher polymedication in elderly asthma. Using a cluster-based approach, we identified three asthma groups sharing similar medication profiles, which were prospectively associated with poor asthma characteristics.

Keywords: asthma; medications; comorbidities; network analysis; drug claims data.

Background

Asthma is a complex and heterogeneous disease, in which inflammatory pathways are involved. Comorbidities are common in asthma, leading to polymedication, particularly in the elderly; a recent study estimated that old people with asthma had eight comorbidities on average versus 3.4 for those in younger adults (75). The most common comorbidities include allergic rhinitis, chronic sinusitis, gastro-oesopheageal reflux disease (GERD), obesity, obstructive sleep apnea syndrome, hormonal and psychological disturbances, lower airway diseases, particularly chronic obstructive pulmonary disease (COPD), and infections (73). Emerging comorbid conditions have been recently proposed, such as diabetes mellitus, metabolic syndrome, and cardiovascular diseases (80). In asthma, comorbidities may affect disease diagnosis, disease control/severity, lung function, health-related quality of life, and asthma medication response, leading to excess medical costs (72, 73, 76-78). Comorbidity-related medications have poorly been addressed in asthma, and never in a comprehensive assessment integrating all medications used by patients (73, 75, 76, 98). To which extent these treatments influence asthma features, prognosis and therapeutic management is sparsely known (74, 80, 81).

New methods based on an integrative approach were developed over the past decade to decipher disease complexity (183). Network models have been recently proposed in two lung diseases, COPD and asthma-COPD overlap syndrome (ACOS) to map comorbidity interrelationships (184, 185). To our knowledge, no study aimed to identify networks of comorbidities relied on drug administrative databases.

We aimed to comprehensively investigate medications associated with asthma-related comorbidities in elderly women, using a pharmacoepidemiological approach relying on drug administrative databases. Specific aims were: i) to characterize and compare the medication

interrelationships among old women with and without asthma, and ii) to comprehensively identify specific comorbidities-related medication profiles in asthma and to prospectively assess their association with asthma characteristics.

Methods

Study population

All women from the Asthma-E3N study were included in this analysis. Briefly, the Asthma-E3N study is a nested case-control study focused on respiratory health within the E3N study (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale [MGEN]), a prospective study focused on major chronic diseases in women belonging to a French national health insurance plan covering mostly teachers. The E3N study (11 questionnaires sent since 1990) and the Asthma-E3N study (2011-2012) provided detailed questionnaires on general features and respiratory health, respectively, completed by a comprehensive outpatient dispensed medication database (MGEN) from 2004 onwards (11, 143). Ever asthma was defined by a single positive answer to the question "Have you ever had an asthma attack?" widely used in epidemiological studies, from 1992 to 2005 and confirmed in the Asthma-E3N study either by a positive answer to this question or by the report of asthma symptoms (9).

Estimation of medication exposure

Drug classes were identified over 24 months from the exhaustive MGEN drug database by the second and the third levels of the Anatomical Therapeutic Chemical code (e.g., R03A for "Adrenergics, inhalants") (171).

Asthma characteristics

Asthma control was assessed by the Asthma Control Test (ACT), covering symptom frequency, rescue therapy use, sleep interference, activity limitation, and self-rating of control, over the last month before the Asthma-E3N questionnaire (5). Subjects were classified into two groups: uncontrolled (ACT ≤19) vs. controlled asthma (ACT >19) (5).

Asthma attack was defined by a positive answer to the single question "Have you had an asthma attack?" over the twelve previous months from the Asthma-E3N questionnaire. An asthma attack lasting at least two days was considered as asthma exacerbation.

Asthma severity was assessed from asthma treatment level according to the GINA (Global Initiative for Asthma) classification over the last 12 months before the Asthma-E3N questionnaire (see Supplemental material, p. 133) (2). Oral corticosteroids were not included in this classification because of their wide-range of indications, particularly in the elderly, as tiotropium introduced in the GINA classification in 2016 as add-on therapy for asthma with a history of exacerbations.

Health-related quality of life was assessed by the specific Asthma Quality of Life Questionnaire (AQLQ), covering four domains ("symptoms", "activity limitation", "emotional function", and susceptibility to "environmental exposure") related to the two previous weeks from the Asthma-E3N questionnaire. The total AQLQ score was computed as the mean of all questions, a lower score being associated with worse health-related quality of life. All AQLQ scores were compared with the minimal clinically important difference (0.5), i.e., the smallest difference considered clinically and socially relevant (157), addressing the magnitude of the differences observed between groups (186).

The ACOS phenotype was defined from the Asthma-E3N questionnaire by a positive answer to the single question "Did a doctor ever tell you that you had one of these COPD

forms: chronic bronchitis, emphysema, COPD (unspecified form)?", already used and validated in a previous study among health professionals (3, 175).

The late-onset asthma phenotype was defined from the Asthma-E3N questionnaire as a disease onset after 40 years old vs. long-standing asthma, with onset in childhood or young adulthood (59, 65).

Sociodemographic and clinical variables

Sociodemographic characteristics assessed at the Asthma-E3N questionnaire included age, body mass index (4 classes: <20, [20-25[, [25-30[, ≥30 $kg.m^2$), education level (4 classes: <baccalaureate, bac.; [bac.; bac. +2]; [bac. +3; bac. +4]; ≥bac. +5), active smoking (3 classes: never, ex- and current smoker), and medical follow-up over the last 12 months (frequency, medical specialty). Asthma-related characteristics included an asthma symptom score measured over the last three months (4 classes: 0, 1, 2 and ≥3) and parental history of asthma (4 classes: none, father, mother and both).

Statistical analysis

Comparisons of qualitative and quantitative variables between groups of subjects were performed by Student's t-test and chi-square test or Fisher's exact test, respectively. All drug classes dispensed to our elderly population were comprehensively displayed by network graphs using Gephi Graph visualization and Manipulation software V-0.9.1 (187). Drug classes (at least one reimbursement identified during the study period) were represented in the graph by a node whose the diameter is proportional to its prevalence in the study population. The relationships between drug classes were estimated by Phi coefficients (Φ) (i.e., Pearson's correlation coefficients for binary variables) and statistical significant associations were represented with edges between nodes in the graph ($p \leq 0.01$ as previously used in the literature) (184, 188, 189).

We performed latent class analysis, a data driven approach, to identify specific asthma groups based on their comorbidities-related medication profiles. In this analysis, we included i) drug classes related to known or emerging asthma-related comorbidities (i.e., A02 "Drugs for acid related disorders" for GERD; R06 "Antihistamines for systemic use" for allergy; R01 "Nasal preparations" for nasal polyps and rhinosinusitis; N05 "Psycholeptics", N06A "Antidepressants", and N06C "Psycholeptics and psychoanaleptics in combination" for psychological disturbances; J01 "Antibacterials for systemic use", J02 "Antimycotics for systemic use", J04 "Antimycobacterials", and J05 "Antivirals" for infections; G03 "Sex hormones and modulators of the genital system" for hormonal disturbances; A10 "Drugs used in diabetes" for diabetes; C01 "Cardiac therapy", C02 "Antihypertensives", C03 "Diuretics", C04 "Peripheral vasodilatators", C07 "Beta blocking agents", C08 "Calcium channel blockers", and C09 "Agents acting on the renin-angiotension system" for cardiovascular diseases; C10 "Lipid modifying agents" for dyslipidemia which is included in metabolic syndrome with hypertension and diabetes), ii) the potential new drug classes linked with asthma-related medications identified by the network graphs, and iii) clinical and environmental factors which cannot be assessed by drug classes (i.e., body mass index for obesity, diagnosis reported by the respondents for obstructive sleep apnea syndrome, and smoking). Regular medication exposure was defined as at least six reimbursements of a drug class over the period, intermittent exposure as from three to five reimbursements, and unexposure as less than three reimbursements in LCA. Analysis of the medication profiles derived from LCA was performed by logistic regressions for qualitative variables and linear regressions for quantitative variables, weighted by the posterior probability of belonging to the cluster. A stratified analysis was performed according to disease activity (current and past asthma). Sensitive analyses were performed with the same number of women with vs. without asthma and women with current vs. past asthma to allow comparisons of p-values between the

groups. Analyses were performed using the SAS 9.4 statistical software (SAS Institute, Cary, NC, USA).

Results

Study population

The Asthma-E3N study included 4,328 women with ever asthma (Figure 15). As compared to women without asthma (n = 13,130), women with ever asthma were slightly younger (69.6 ± 6.1 vs. 70.1 ± 6.3 years old, p <0.0001), more often obese (9.9% vs. 6.3%, p <0.0001), more often never/ex-smokers (96.1% vs. 95.3%, p <0.0001), and had a higher education level (>bac. +2: 40.0% vs. 36.0%, p <0.0001). Among women with ever asthma, 94.2% used other medications than for asthma during the study period. Women using medications among asthma-unrelated drug classes were older, had a higher education level and were less medically monitored, as compared to those not using such treatments (Table X). Women with current asthma (n = 3,023) were older, more often obese and less medically followed, as compared to women with past asthma.

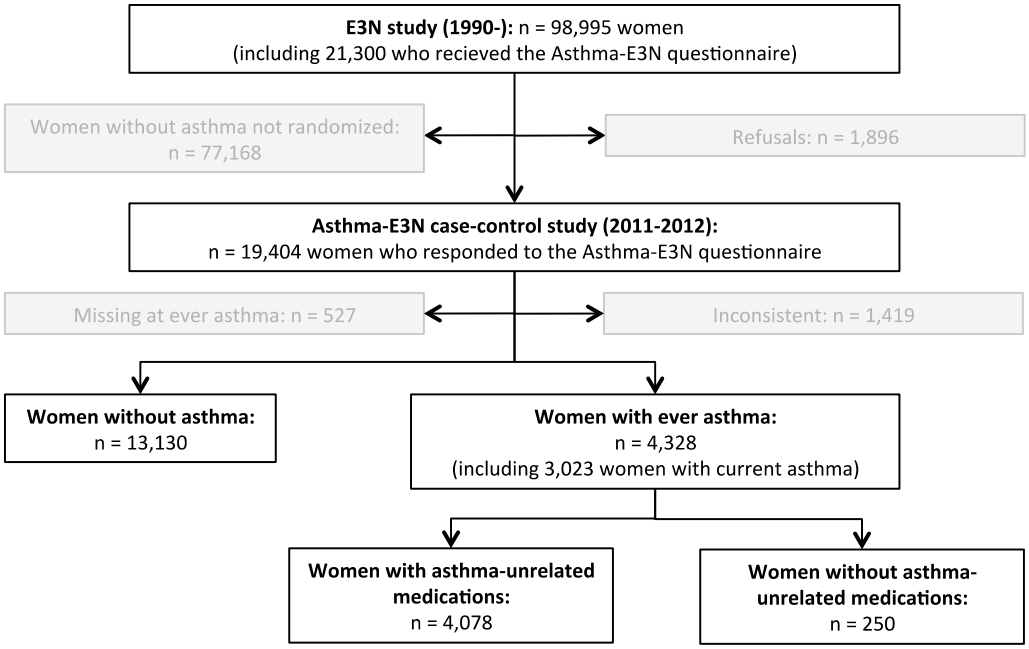


Figure 15. Flowchart of the study population.

Table X. Characteristics of women with ever asthma from the Asthma-E3N study, according to the use of asthma-unrelated medications and the disease activity.

Variable		Whole population (n = 4,328)		Women with asthma-unrelated medications (n = 4,078)		Women without asthma-unrelated medications (n = 250)		Women with current asthma (n = 3,023)		Women with past asthma (n = 1,305)		p value*	p value**
Socio-demographic characteristics													
Age (years), mean ± SD		69.6	± 6.1	69.4	± 6.0	71.3	± 7.1	69.9	± 6.1	69.1	± 6.0	<0.0001	0.0001
BMI (kg/m²), n (%)	<20	431	(10.9)	406	(10.9)	25	(11.2)	287	(10.4)	144	(12.1)	0.78	<0.0001
	20≤ BMI <25	2,082	(52.9)	1,968	(53.0)	114	(50.9)	1,354	(49.2)	728	(61.4)		
	25≤ BMI <30	1,035	(26.3)	970	(26.1)	65	(29.0)	775	(28.2)	260	(21.9)		
	≥30	389	(9.9)	369	(9.9)	20	(8.9)	335	(12.2)	54	(4.5)		
Education level, n (%)	<baccalaureate	449	(10.8)	367	(9.3)	82	(34.2)	319	(11.0)	130	(10.3)	<0.0001	0.08
	Bac. – bac. +2	2,050	(49.2)	1,974	(50.3)	76	(31.7)	1,462	(50.3)	588	(46.7)		
	Bac. +3 – bac. + 4	840	(20.2)	800	(20.4)	40	(16.7)	562	(19.3)	278	(22.1)		
	≥bac. +5	826	(19.8)	784	(20.0)	42	(17.5)	564	(19.4)	262	(20.8)		
Smoking, n (%)	Never smoker	2,152	(50.1)	2,028	(50.1)	124	(50.6)	1,494	(49.9)	658	(50.8)	0.96	0.45
	Ex-smoker	1,975	(46.0)	1,864	(46.1)	111	(45.3)	1,380	(46.0)	595	(45.9)		
	Current smoker	166	(3.9)	156	(3.8)	10	(4.1)	123	(4.1)	43	(3.3)		
Asthma													
Asthma symptoms, n (%)	0	1,248	(37.5)	1,180	(37.5)	68	(37.4)	177	(7.8)	1,071	(100.0)	0.29	<0.0001
	1	891	(26.7)	849	(26.9)	42	(23.1)	891	(39.4)	0	(0.0)		
	2	488	(14.6)	464	(14.7)	24	(13.2)	488	(21.6)	0	(0.0)		
	≥3	705	(21.2)	657	(20.9)	48	(26.4)	705	(31.2)	0	(0.0)		
Parental asthma, n (%)	None	3,071	(76.2)	1,905	(76.2)	166	(75.1)	2,104	(75.2)	967	(78.5)	0.34	0.03
	Father	454	(11.3)	424	(11.1)	30	(13.6)	321	(11.5)	133	(10.8)		
	Mother	437	(10.8)	413	(10.8)	24	(10.9)	317	(11.3)	120	(9.7)		
	Both	69	(1.7)	68	(1.8)	1	(0.5)	57	(2.0)	12	(1.0)		
Medical follow-up over the last 12 months, n (%)		1,306	(33.1)	1,216	(32.7)	90	(40.5)	1,220	(44.9)	86	(7.0)	0.02	<0.0001
Regular monitoring for asthma, n (%)		733	(18.3)	684	(18.1)	49	(22.3)	683	(24.7)	50	(4.0)	0.11	<0.0001
General practitioner, n (%)		1,188	(30.9)	1,105	(30.5)	83	(38.4)	1,100	(41.9)	88	(7.2)	0.01	<0.0001
Consultant, n (%)		826	(21.7)	765	(21.2)	61	(29.8)	757	(29.3)	69	(5.6)	0.04	<0.0001

Bac, baccalaureate; BMI, Body Mass Index; SD, standard deviation.

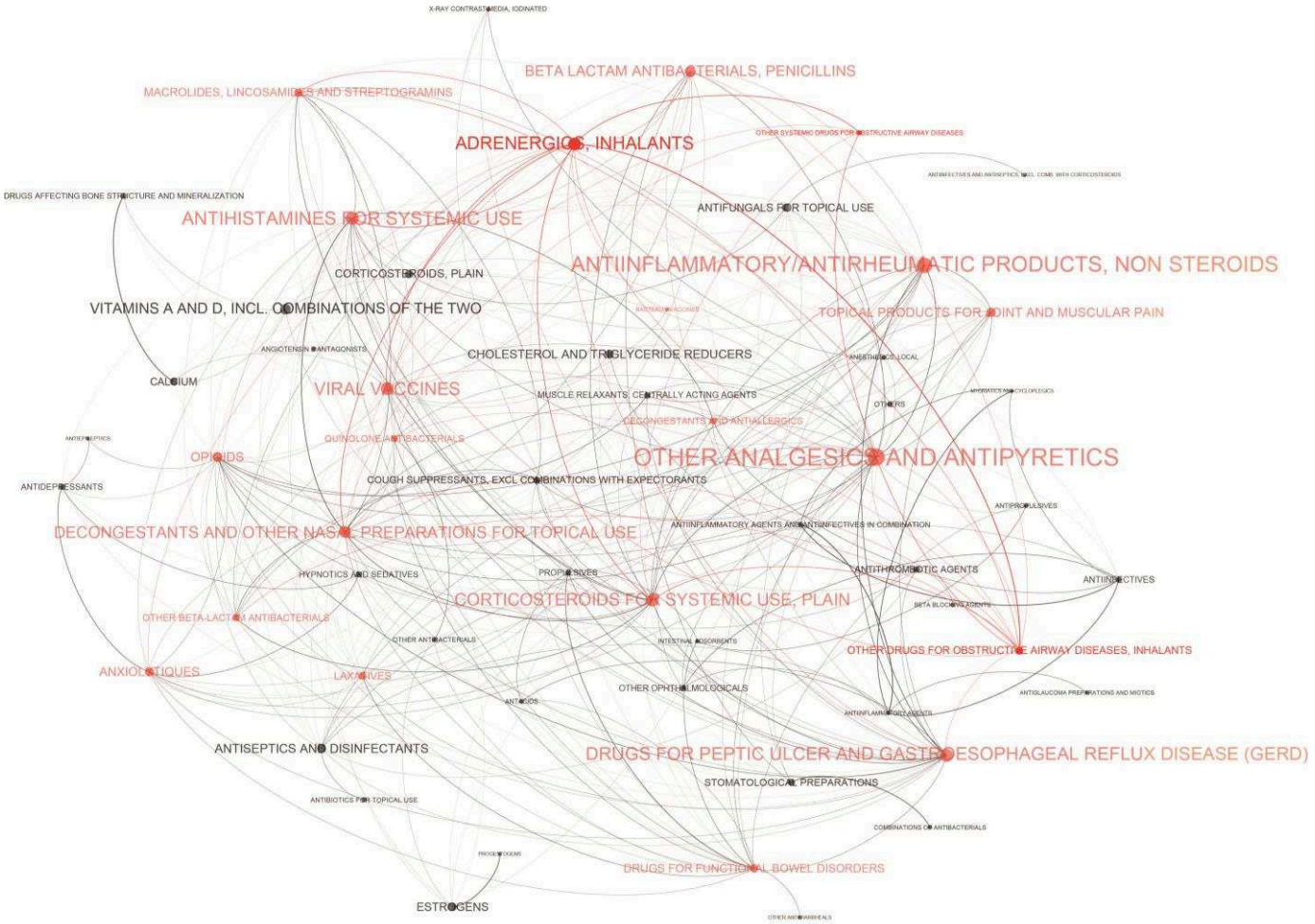
* p value comparing women with comorbid conditions and women without comorbid conditions.

** p value comparing women with current asthma and women with past asthma.

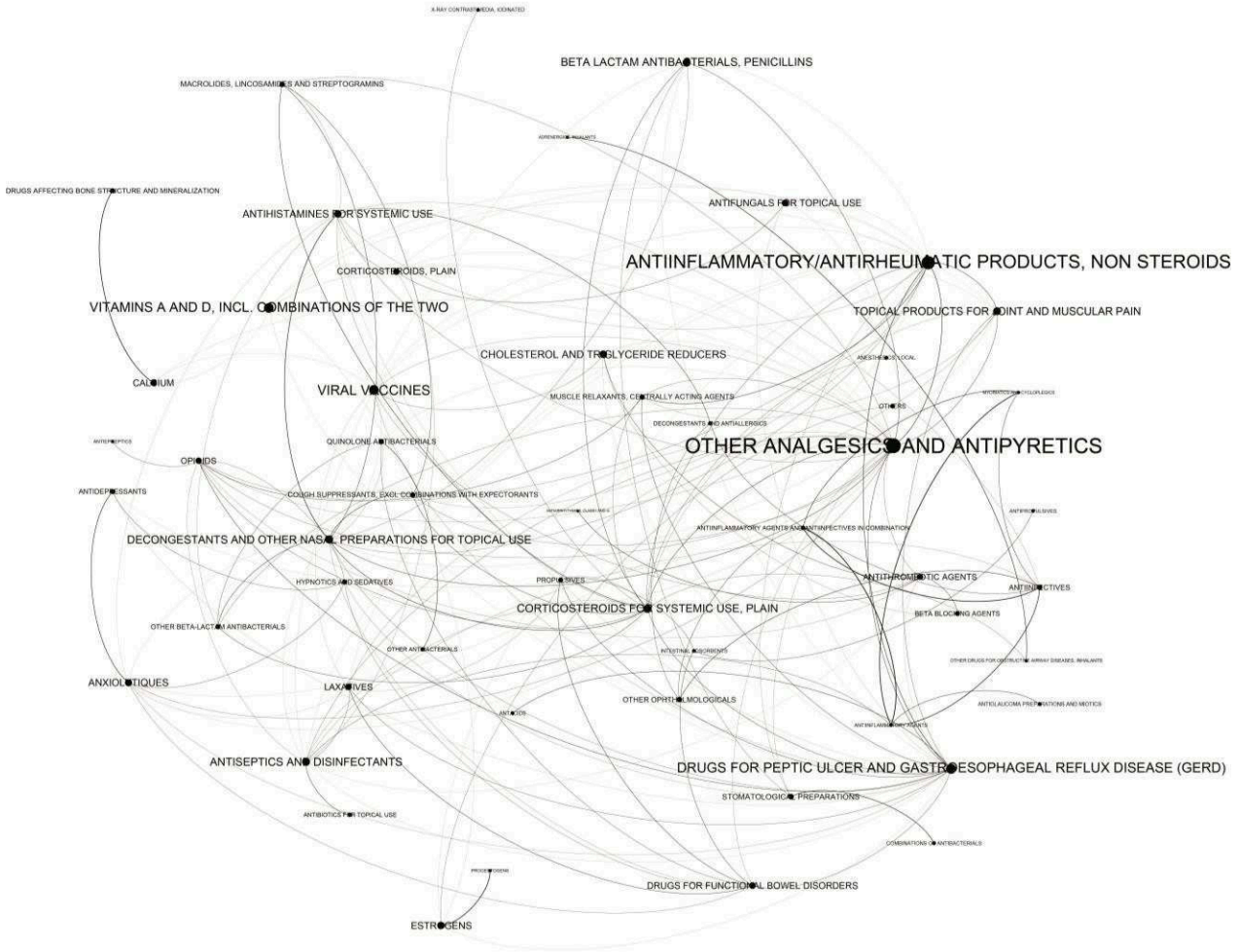
Network analysis: "Pharmacome" in asthma

The Pharmacome in asthma included similar drug classes as the Pharmacome in women without asthma (177 vs. 171, respectively), but showed a more complex network with more links (282 vs. 160 statistically significant links, respectively) (Figure 16 and see Table S1 in Supplemental material, p. 134). Among the 265 drug classes from the third level of the ATC classification, the main drug classes reimbursed in women with ever asthma were respectively: N02B "Other analgesics and antipyretics" (72.2% of women), M01A "Antiinflammatory and antirheumatic products" (63.6%), R06A "Antihistamines for systemic use" (52.7%), A02B "Drugs for peptic ulcer and gastro-oesophageal reflux disease" (51.5%), J07B "Viral vaccines" (50.2%), and R03A "Adrenergics, inhalants" (50.1%). Among the 282 statistically significant links found between drug classes (Φ ranged from 0.08 to 0.43, median [$Q_{25\%}$;$Q_{75\%}$], 0.16 [0.13;0.21]), 31 links associated asthma drug classes with other drug classes (Φ ranged from 0.09 to 0.40, median [$Q_{25\%}$;$Q_{75\%}$], 0.17 [0.14;0.22]) (Figure 16). The drug classes were: Corticosteroids for systemic use (ATC code, H02A; Φ = 0.29), Antiinfectives (ATC codes, J01C, J01D, J01F, J01M, J07A and J07B; Φ = 0.29), Antihistaminics for systemic use (ATC code, R06A; Φ = 0.28), Topical decongestants (ATC codes, R01A and S01G; Φ = 0.27), Drugs for GERD (ATC code, A02B; Φ = 0.18), Analgesics (ATC codes, N02A and NO2B; Φ = 0.14), Anxiolytics (ATC codes, N02A and NO2B; Φ = 0.14), Drugs for bowel diseases (ATC codes, A03A and A06A; Φ = 0.12), and Antiinflammatory/antirheumatic drugs (ATC codes, M01A and M02A; Φ = 0.10). The stratified analysis according to disease activity showed that the prevalence and number of simultaneous drug classes were higher in women with current asthma than in those with past asthma (See Figure S1 in Supplemental material, p. 135). A sensitive analysis among 1,305 women with current asthma randomly selected showed similar results, indicating that the

different patterns observed between current and past asthma were not driven by the unbalanced sample sizes (data not shown).


X-RAY CONTRAST MEDIA, IODINATED
BETA LACTAM ANTIBACTERIALS, PENICILLINS
MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
ADRENERGICS, INHALANTS
OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
ANTIINFECTIVES AND ANTISEPTICS, EXCL. COMB. WITH CORTICOSTEROIDS
DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION
ANTIHISTAMINES FOR SYSTEMIC USE
ANTIFUNGALS FOR TOPICAL USE
CORTICOSTEROIDS, PLAIN
ANTIINFLAMMATORY/ANTIRHEUMATIC PRODUCTS, NON STEROIDS
VITAMINS A AND D, INCL. COMBINATIONS OF THE TWO
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN
ANGIOTENSIN II ANTAGONISTS
CHOLESTEROL AND TRIGLYCERIDE REDUCERS
ANESTHETICS, LOCAL
CALCIUM
VIRAL VACCINES
MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS
OTHERS
DECONGESTANTS AND ANTIALLERGICS
ANTISEPTICS
QUINOLONE ANTIBACTERIALS
OPIOIDS
OTHER ANALGESICS AND ANTIPYRETICS
ANTIDEPRESSANTS
COUGH SUPPRESSANTS, EXCL COMBINATIONS WITH EXPECTORANTS
ANTIPROPULSIVES
DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE
ANTIINFLAMMATORY AGENTS AND ANTIINFECTIVES IN COMBINATION
HYPNOTICS AND SEDATIVES
PROPULSIVES
ANTITHROMBOTIC AGENTS
ANTIINFECTIVES
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
BETA BLOCKING AGENTS
OTHER BETA-LACTAM ANTIBACTERIALS
OTHER ANTIBACTERIALS
INTESTINAL ADSORBENTS
OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS
ANXIOLYTIQUES
LAXATIVES
OTHER OPHTHALMOLOGICALS
ANTIGLAUCOMA PREPARATIONS AND MIOTICS
ANTACIDS
ANTIINFLAMMATORY AGENTS
ANTISEPTICS AND DISINFECTANTS
DRUGS FOR PEPTIC ULCER AND GASTRO-ESOPHAGEAL REFLUX DISEASE (GERD)
STOMATOLOGICAL PREPARATIONS
ANTIBIOTICS FOR TOPICAL USE
COMBINATIONS OF ANTIBACTERIALS
PROGESTOGENS
DRUGS FOR FUNCTIONAL BOWEL DISORDERS
ESTROGENS
OTHER ANTIDIARRHEALS

(a)

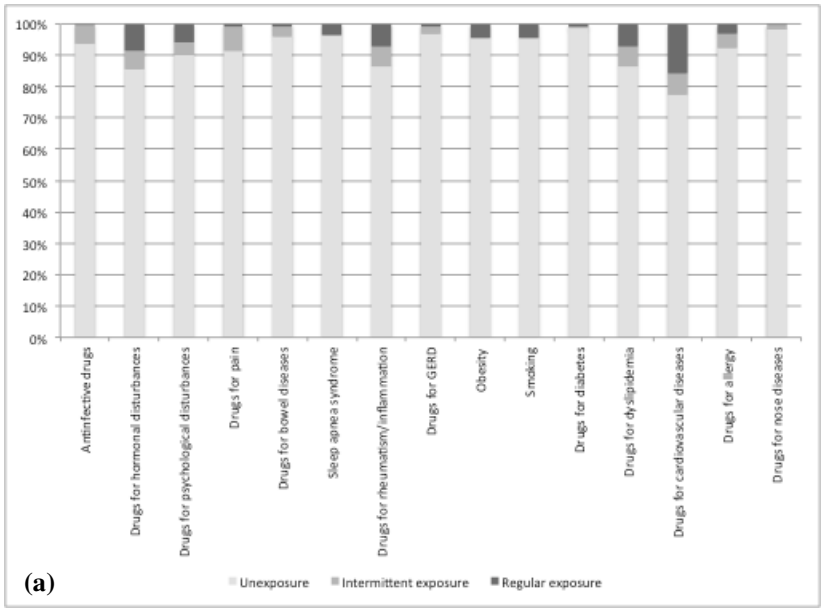


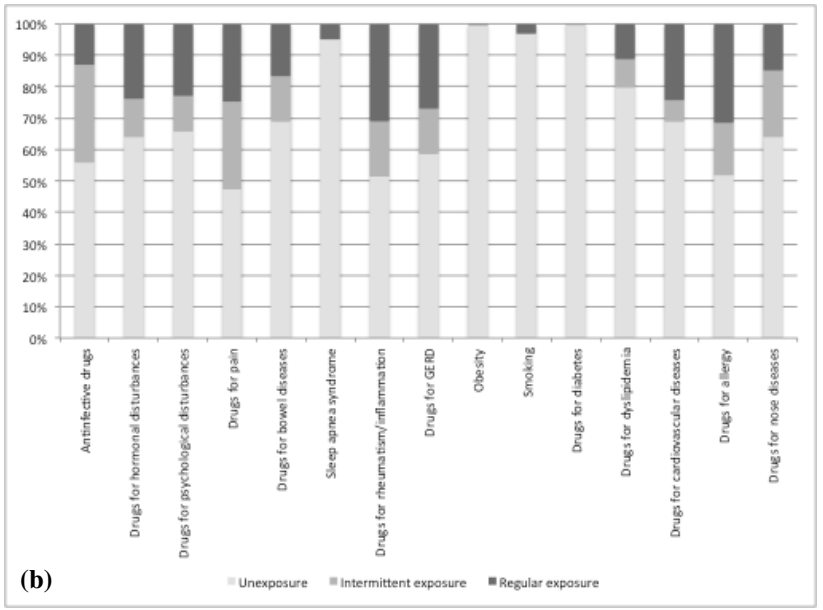
(b)

Figure 16. Pharmacome among **(a)** the 4,328 elderly women with ever asthma and **(b)** 4,328 women without asthma randomly selected from the Asthma-E3N study. Network graph were built from all drug classes according to the third level of the ATC classification. Nodes' diameter represents the prevalence of the drug class in our population. Edges' thickness is related to the strength of the association between two drug classes estimated by Phi coefficient. The statistical significant links between asthma drug classes and other drug classes are highlighted in red in graph **(a)**.

“Pharmacome” and asthma characteristics

Latent class analysis, including both clinical/environmental factors associated to asthma, drug classes linked to known asthma-related comorbidities and those identified by the network graph (15 variables including 12 drug classes), identified three groups of women with ever asthma: a) Cluster No 1, women with few other medications than those for asthma and clinical/environmental factors related to asthma, labeled “Few comorbity-related medications” (n = 2,170, 50.1%); b) Cluster No 2, women taking medications for allergy, nose diseases, rheumatism/inflammation, pain, infections, bowel diseases and hormonal disturbances, labeled “Predominant allergy-related medications” (n = 1,166, 27.0%); and c) Cluster No 3, women more often obese with obstructive sleep apnea syndrome and taking medications for GERD, rheumatism/inflammation, pain, bowel diseases, psychological disturbances, cardiovascular diseases, diabetes and dyslipidemia, labeled “Predominant cardiovascular-related medications” (n = 992, 22.9%) (Figure 17). The mean probability of belonging to the assigned cluster was 0.82 ± 0.17. Compared to the two other clusters (“Few comorbity-related medications” and “Predominant allergy-related medications”), women belonging to the “Predominant cardiovascular-related medications” cluster were older (71.8 ± 6.5 vs. 69.3 ± 5.8 and 68.8 ± 5.8 years, respectively; p <0.0001) and had a lower education level (>bac.+3: 30.7% vs. 44.1 and 40.2%, respectively; p <0.0001). Women belonging to the “Predominant allergy-related medications” cluster had more often drugs for infections and hormonal disturbances than those belonging to the “Predominant cardiovascular-related medications” cluster (Figure 17).





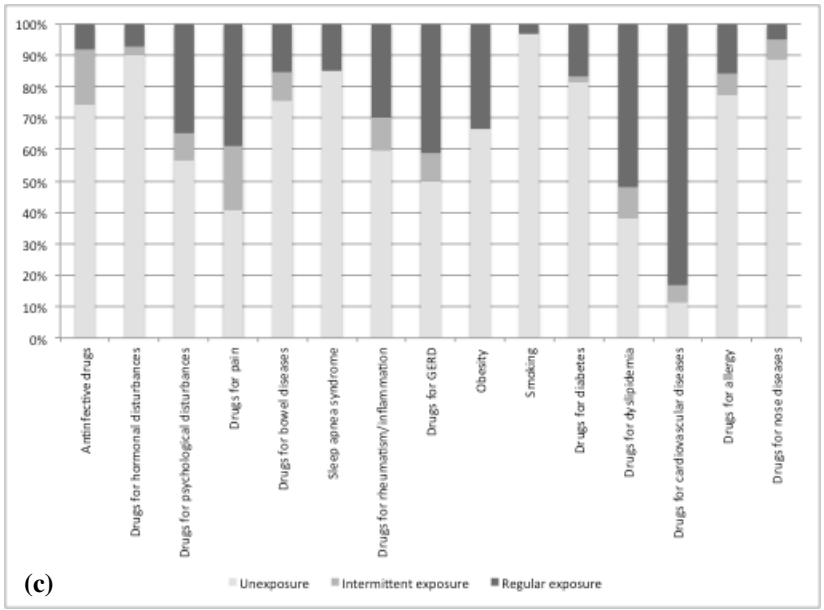


Figure 17. Clusters identified by latent class analysis: a) Cluster No 1, women with few other medications than those for asthma and clinical/environmental factors related to asthma, labeled "Few comorbity-related medications" (n = 2,170, 50.1%); b) Cluster No 2, women taking medications for allergy, nose diseases, rheumatism /inflammation, pain, infections, bowel diseases and hormonal disturbances, labeled "Predominant allergy-related medications" (n = 1,166, 27.0%); and c) Cluster No 3, women more often obese with obstructive sleep apnea syndrome and taking medications for gastro-oesophageal reflux diseases, rheumatism /inflammation, pain, bowel diseases, psychological disturbances, cardiovascular diseases, diabetes and dyslipidemia, labeled "Predominant cardiovascular-related medications" (n = 992, 22.9%).

Compared to women belonging to the "Few comorbity-related medications" cluster, women belonging to the two other clusters had more often uncontrolled asthma, asthma attacks and exacerbations, had a higher level of asthma treatment and a later age at asthma-onset (Table XI and Figure 18). The total AQLQ score was lower in women belonging to the "Predominant allergy-related medications" (ß = 5.94 ± 0.03, p <0.0001) and "Predominant cardiovascular-related medications" clusters (ß = 5.71 ± 0.04, p <0.0001). Similar magnitudes of the estimates were found when adjusting on age.

Asthma severity, defined by asthma treatment level at steps 4 and 5 according to the GINA classification, significantly varied across the medication profiles from 7.0% to 21.8% (Table XI). The regression model adjusted on disease severity showed similar patterns of association, although the association with asthma exacerbation became only borderline significant (See Table S2 in Supplemental material, p. 136).

Table XI. Description of the asthma characteristics according to the clusters identified by latent class analysis.

Asthma characteristic	Whole population (n = 4,328)	Cluster No 1 (n = 2,170)	Cluster No 2 (n = 1,166)	Cluster No 3 (n = 992)	p value
Asthma control					
Uncontrolled asthma, n (%)	522 (19.2)	184 (14.7)	162 (20.6)	176 (26.2)	<0.0001
Asthma symptoms					
At least one asthma attack, n (%)	1,055 (25.4)	433 (20.7)	324 (29.1)	298 (31.5)	<0.0001
At least one asthma exacerbation, n (%)	446 (13.2)	174 (10.6)	149 (16.1)	123 (15.3)	0.004
Asthma severity					
High level of asthma treatment *, n (%)	604 (14.0)	153 (7.0)	254 (21.8)	197 (19.9)	<0.0001
Asthma onset					
Late asthma onset, n (%)	2,693 (68.0)	1,294 (64.7)	760 (69.8)	639 (73.1)	<0.0001
Asthma-COPD overlap syndrome					
COPD, n (%)	863 (22.7)	338 (17.7)	266 (25.9)	259 (30.1)	<0.0001
Health-related quality of life					
Total AQLQ score, m ± sd	6.0 ± 1.0	6.2 ± 0.9	5.9 ± 1.0	5.7 ± 1.1	<0.0001

Cluster No 1, labeled "Few comorbidity-related medications" cluster; Cluster No 2, labeled "Predominant allergy-related medications" cluster; Cluster No 3, labeled "Predominant cardiovascular-related medications" cluster. AQLQ, Asthma Quality of Life Questionnaire; COPD, Chronic obstructive pulmonary disease.

* Steps 4 and 5 according to the GINA classification.

The “Few comorbity-related medications”, “Predominant allergy-related medications” and “Predominant cardiovascular-related medications” clusters included 62.9%, 74.0% and 80.2% of women with current asthma, respectively ($p < 0.0001$). The stratified analysis showed similar associations between the medication profiles and asthma characteristics among women with current asthma than among those in the whole population, but discrepancies were found among women with past asthma, probably partly due to the reduced sample size leading to a decreased statistical power in this group (see Table S3 in Supplemental material, p. 137).

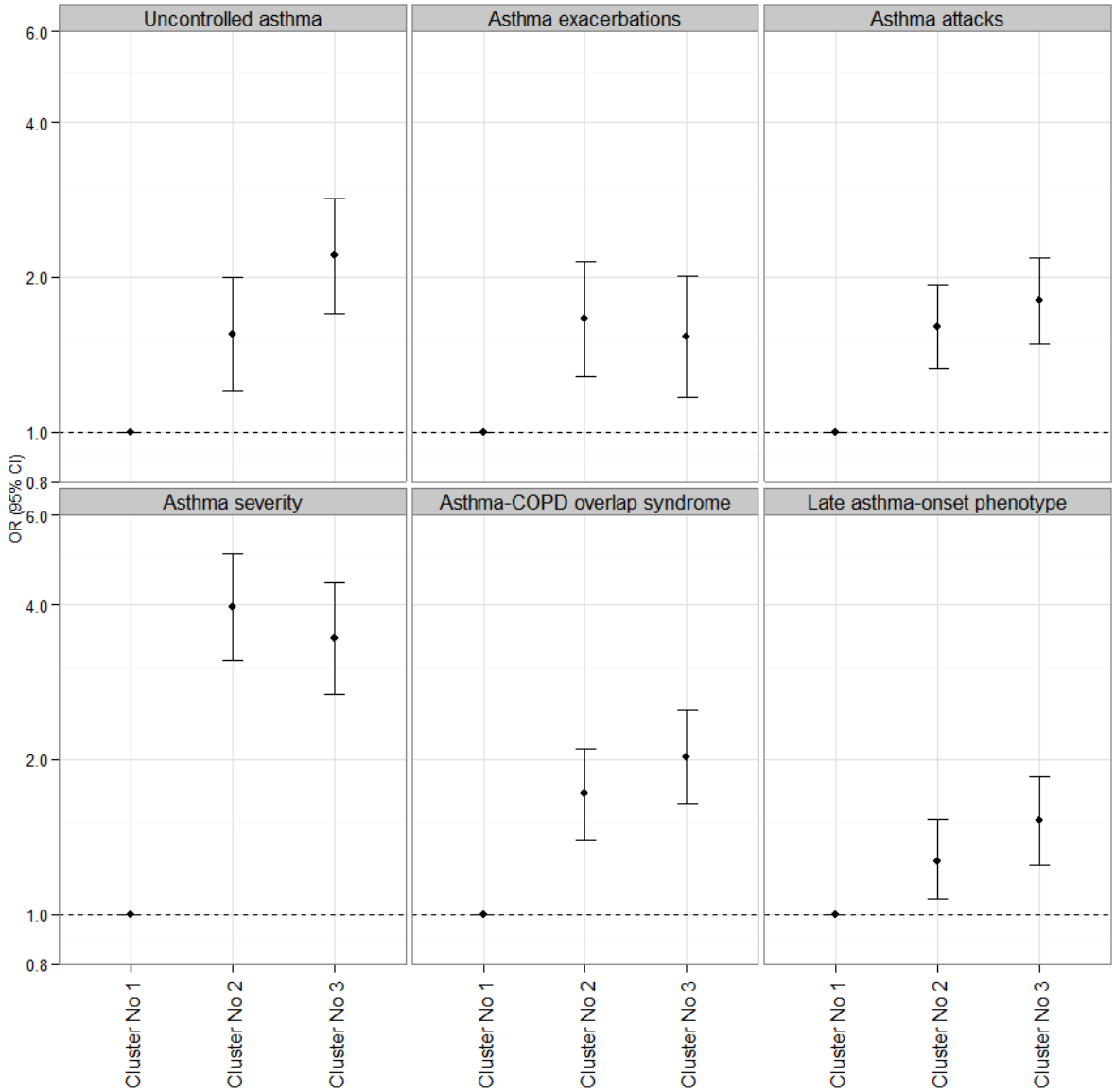


Figure 18. Associations between groups identified by latent class analysis and asthma characteristics. a) Cluster No 1, women with few other medications than those for asthma and clinical/environmental factors related to asthma, labeled "Few comorbity-related medications" (n = 2,170, 50.1%); b) Cluster No 2, women taking medications for allergy, nose diseases, rheumatism /inflammation, pain, infections, bowel diseases and hormonal disturbances, labeled "Predominant allergy-related medications" (n = 1,166, 27.0%); and c) Cluster No 3, women more often obese with obstructive sleep apnea syndrome and taking medications for gastro-oesophageal reflux diseases, rheumatism/inflammation, pain, bowel diseases, psychological disturbances, cardiovascular diseases, diabetes and dyslipidemia, labeled "Predominant cardiovascular-related medications" (n = 992, 22.9%).

Discussion

To our knowledge, this is the first study using a pharmacoepidemiological approach relying on drug administrative databases to characterize asthma comorbidities. We built the "Pharmacome" in asthma, which showed a more complex medication network with a larger number of associations, as compared to observations among women without asthma. Using a cluster-based approach, we identified three asthma groups, characterized by specific medication profiles, prospectively associated with poorly controlled asthma.

This study focused on the elderly, a population of particular interest in terms of multimorbidity, and so polymedication. More than half of the population over 65 years old suffers from multimorbidity (i.e., at least two chronic diseases), leading to a five-time increase in healthcare expenditures compared to non-multimorbid people (69, 70). Our findings relying on a population of elderly women with asthma cannot be directly extrapolated to men, but are still of public health relevance because of higher asthma prevalence and severity in elderly women, as compared to men (64).

One of the major strengths of this study lies on the comprehensive drug dispensed database from 2004 onwards, allowing to describe the "Pharmacome" among elderly women. Already used in several countries for drug surveillance, administrative databases are a unique and powerful source of data to estimate drug use in real life among very large populations (102). Our study expands the opportunity of such databases by supporting their interest in identifying groups of women sharing similar medication profiles. We acknowledge that medications are a substitute of the diagnosis made by a physician and that drug dispensed database might not accurately assess diseases in some contexts. However, the ATC classification used in our study is a standardized and validated classification according to the main therapeutic indication of medications, recommended and promoted by the World Health

Organization (171). The detailed individual and phenotypic characteristics provided by the Asthma-E3N questionnaire offers the unique opportunity to assess the prospective associations between medications and asthma characteristics.

The medication network offers an integrative approach to understand complex diseases, such as asthma. Most of studies suffer from a reductionist approach considering few diseases, leading to potential missing associations with other diseases (188). Few studies have considered lung diseases as an integrative system, and none specifically by a pharmacoepidemiological approach (183, 188, 190). Using an unbiased approach, we built the "Pharmacome" in asthma allowing to visualize the complex medication network exhibiting the prevalence of treatments for specific drug classes and their connections. Our findings confirm that polymedication is common in ambulatory care for old people, and particularly in the elderly with current asthma (191, 192). Our approach relying on a population with ever asthma covers a wide range of asthma phenotypes, and allows us to address the role of disease activity and severity in our study. We showed that disease severity was associated with more polymediation, but we failed to find connections with asthma drug classes and therapeutic classes associated with some asthma-related comorbidities (i.e., hormonal disturbances, cardiovascular diseases, diabetes and dyslipidemia) (73, 80). This may be explained by the fact that these drugs are related to asthma, but among women with ever asthma they are not associated with disease severity. We acknowledge that drug administrative databases are a proxy of medication use and medication exposure may be hampered by non-adherence commonly encountered, especially in chronic diseases (161). This weakness is difficult to avoid, but is probably minimized in our study conducted on highly educated women.

Clustering methods are increasingly used in epidemiological research to identify patients' profiles sharing similar characteristics. In our study, we applied latent class analysis, a data driven approach, including both drug classes related to asthma comorbidities reported

in the literature and those identified by the network graph. Three clinically relevant clusters of elderly women with ever asthma were identified. A large part of our population (50.1%) had few comorbidity-related medications. About one fourth of our elderly population belonged to the "Predominant allergy-related medications" cluster. As expected, this frequency is much lower as compared to observations relying on either skin prick test or IgE measurements to assess allergy in younger adults, which showed that about two-third of adults with ever asthma had allergic-related phenotypes (193). The last cluster identified women with a high proportion of cardiovascular-related medications, including drugs for diabetes, dyslipidemia and cardiovascular diseases. Subjects with asthma, especially adult-onset asthma women, are at higher risk for cardiovascular comorbidities (194, 195). However, the relationship between asthma and cardiovascular diseases remains controversial (80). The role of asthma medications to prevent or enhance the risk of cardiovascular diseases remains unknown. Finally, a novelty of this study relies on the relationship between asthma severity and rheumatism/inflammation in the two polymedicated clusters. Common pathogenesis pathway between these two syndromes (e.g., IFN gamma, T cells, IL-17) provides biological plausibility of our observation (196, 197).

As recently shown, the coexistence of medications may hampered asthma control (81). As compared to the cluster "Few comorbidity-related medications", the two other clusters characterized by polymedication had a higher risk for subsequent poor asthma characteristics (uncontrolled asthma, poor health-related quality of life, severe asthma, asthma attacks/exacerbations). Our results observed in women with ever asthma were consistent with those observed in women with current asthma but not with those observed in women with past asthma, confirming that the coexistence of polymedication, proxy of comorbidities, is associated with disease activity (73). The two clusters characterized by the polymedication were associated with more severe asthma, but the associations between the clusters and the

subsequent asthma characteristics were observed independently from disease severity, suggesting that other factors than asthma severity are involved in this association. Various ways by which comorbidities might impact asthma have been proposed (e.g., comorbidities might be involved in similar pathophysiological pathways, impact disease evolution or modulate asthma phenotype) but are not fully elucidated (2, 73, 76).

In conclusion, we provide a new insight to decipher asthma complexity. Using the "Pharmacome" as an integrative approach, we showed that polymedication is often encountered among elderly women reported to have ever had asthma. We identified three clinically relevant medication profiles, highlighting that polymedicated patients with ever asthma are at increased risk for subsequent poor asthma prognosis and should be particularly monitored.

Supplemental material

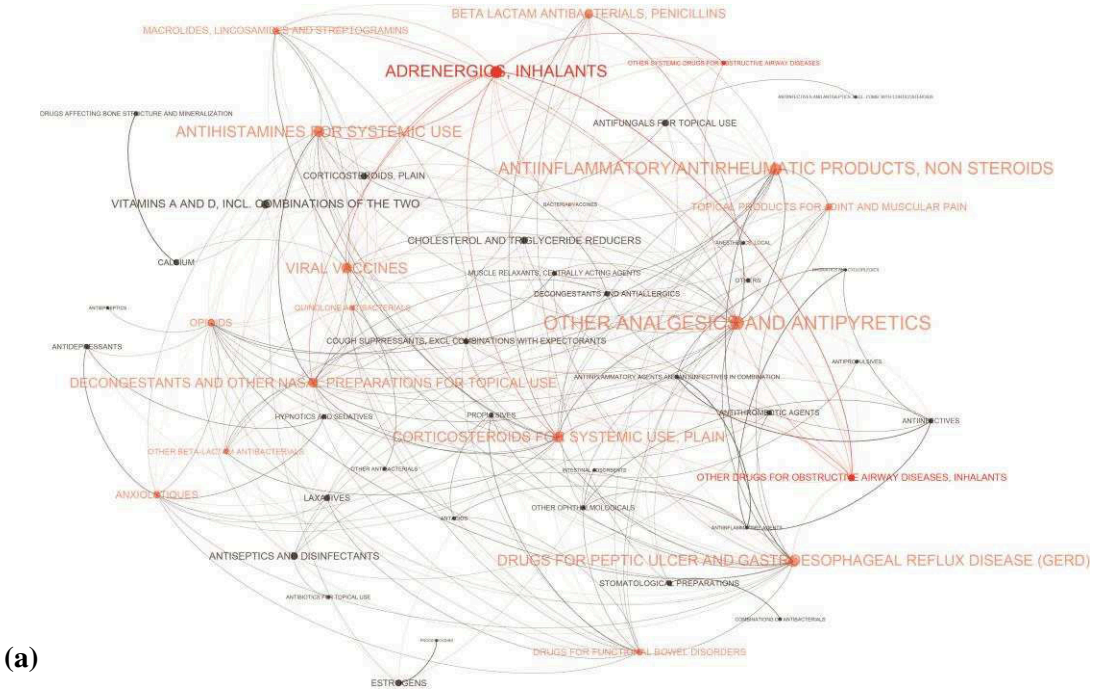
Methods

Asthma characteristics. Asthma severity was assessed from asthma treatment level according to the GINA 2016 classification: 1) Step 1, regular use of inhaled corticosteroids (ICS) or leukotriene receptor antagonists (LTRA) (≥4 reimbursements over the last 12 months before the Asthma-E3N questionnaire) but not enough to be defined as daily asthma maintenance therapy, 2) Step 2, low daily dose of ICS or LTRA or xanthines alone, 3) Step 3, either a) low daily dose of ICS associated with long-acting beta$_2$-agonists or LTRA or theophylline or b) medium/high daily dose of ICS, 4) Step 4, medium/high daily dose of ICS associated with long-acting beta$_2$-agonists or high daily dose of ICS associated with LTRA or theophylline, 5) Step 5, add-on treatment. Oral corticosteroids were not included in this classification because of their wide-range of indications, particularly in the elderly, as tiotropium introduced in the GINA 2016 classification as add-on therapy for asthma with a history of exacerbations.

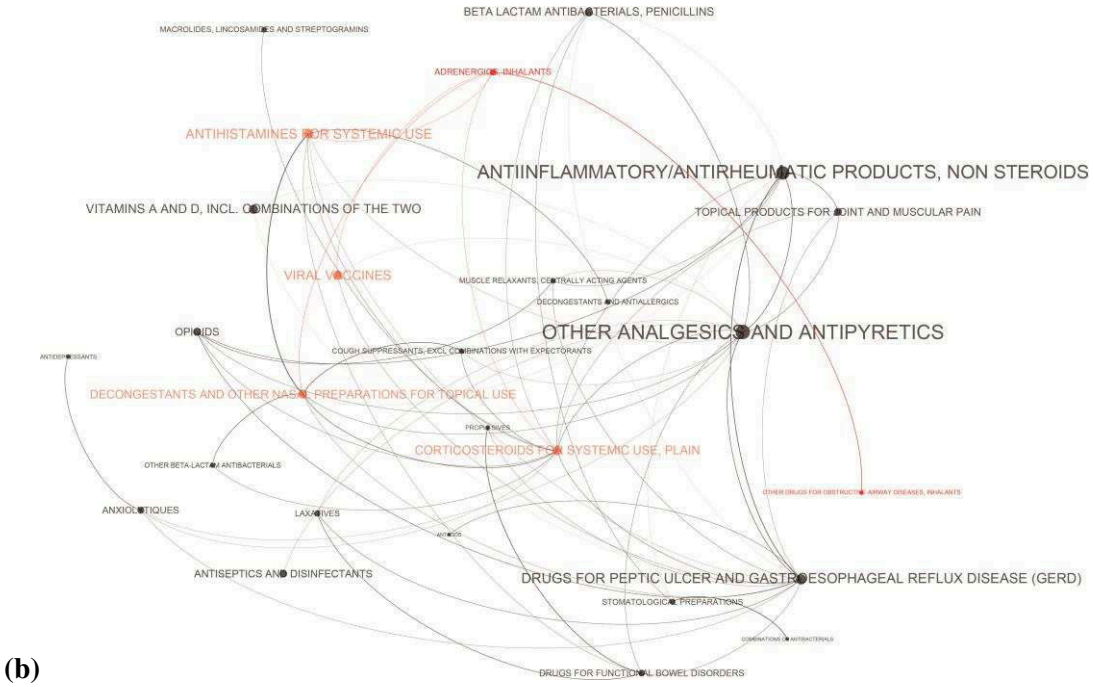
Results

Table S1. Comparison of the twenty drug classes the most reimbursed among women with ever asthma and women without asthma from the Asthma-E3N study.

Women with ever asthma (n = 4,328)				Women without asthma (n = 13,130)			
ATC code	Label	n	(%)	ATC code	Label	n	(%)
N02B	Other analgesics and antipyretics	3,126	(72.2)	N02B	Other analgesics and antipyretics	8,995	(68.5)
M01A	Antiinflammatory/antirheumatic products, non steroids	2,751	(63.6)	M01A	Antiinflammatory/antirheumatic products, non steroids	7,957	(60.6)
R06A	Antihistamines for systemic use	2,280	(52.7)	J07B	Viral vaccines	5,485	(41.8)
A02B	Drugs for peptic ulcer and gastroesophageal reflux disease (GERD)	2,231	(51.5)	A02B	Drugs for peptic ulcer and gastroesophageal reflux disease (GERD)	5,475	(41.7)
J07B	Viral vaccines	2,171	(50.2)	A11C	Vitamins A and D, inclunding combinations of the two	5,125	(39.0)
R03A	Adrenergics, inhalants	2,169	(50.1)	H02A	Corticosteroids for systemic use, plain	4,332	(33.0)
H02A	Corticosteroids for systemic use, plain	2,071	(47.9)	J01C	Beta lactam antibacterials, penicillins	4,314	(32.9)
R01A	Decongestants and other nasal preparations for topical use	1,941	(44.8)	D08A	Antiseptics and disinfectants	4,197	(32.0)
J01C	Beta lactam antibacterials, penicillins	1,743	(40.3)	R01A	Decongestants and other nasal preparations for topical use	4,128	(31.4)
A11C	Vitamins A and D, inclunding combinations of the two	1,724	(39.8)	M02A	Topical products for joint and muscular pain	4,016	(30.6)
M02A	Topical products for joint and muscular pain	1,476	(34.1)	C10A	Cholesterol and triglyceride reducers	3,876	(29.5)
N02A	Opioids	1,459	(33.7)	R06A	Antihistamines for systemic use	3,805	(29.0)
N05B	Anxiolytics	1,400	(32.3)	G03C	Estrogens	3,613	(27.5)
D08A	Antiseptics and disinfectants	1,397	(32.3)	N05B	Anxiolytics	3,473	(26.4)
C10A	Cholesterol and triglyceride reducers	1,353	(31.3)	D01A	Antifungals for topical use	3,303	(25.2)
J01F	Macrolides, lincosamides and streptogramins	1,261	(29.1)	A03A	Drugs for functional bowel disorders	3,232	(24.6)
G03C	Estrogens	1,258	(29.1)	A12A	Calcium	3,220	(24.5)
A03A	Drugs for functional bowel disorders	1,250	(28.9)	D07A	Corticosteroids, plain	3,210	(24.4)
D07A	Corticosteroids, plain	1,222	(28.2)	A06A	Laxatives	3,091	(23.5)
D01A	Antifungals for topical use	1,157	(26.7)	N02A	Opioids	3,049	(23.2)



(a)



(b)

Figure S1. Pharmacome in elderly women with asthma according to disease activity: **(a)** Pharmacome in women with current asthma (n = 3,023) and **(b)** Pharmacome in women with past asthma (n = 1,305). Network graphs were built from all drug classes according to the third level of the ATC classification. Nodes' diameter represents the prevalence of the drug class in our population. Edges' thickness is related to the strength of the association between two drug classes estimated by Phi coefficient. The statistical significant links between asthma drug classes and other drug classes are highlighted in red.

Table S2. Associations between groups identified by latent class analysis and asthma characteristics: a) Cluster No 1, women with few other drug classes than those for asthma and clinical/environmental factors related to asthma, labeled "Few comorbity-related medications"; b) Cluster No 2, women taking drug classes for allergy, nose diseases, rheumatism /inflammation, pain, infections, bowel diseases and hormonal disturbances, labeled "Predominant allergy-related medications"; and c) Cluster No 3, women more often obese with obstructive sleep apnea syndrome and taking drug classes for gastro-oesophageal reflux diseases, rheumatism/inflammation, pain, bowel diseases, psychological disturbances, cardiovascular diseases, diabetes and dyslipidemia, labeled "Predominant cardiovascular-related medications".

Outcomes	Unadjusted model		Adjusted model *	
	OR	[CI95%]	OR	[CI95%]
Uncontrolled asthma				
Cluster No 1	1.00	-	1.00	-
Cluster No 2	1.55	[1.19;2.00]	1.69	[1.29;2.21]
Cluster No 3	2.20	[1.70;2.84]	2.07	[1.81;2.36]
Asthma exacerbations				
Cluster No 1	1.00	-	1.00	-
Cluster No 2	1.66	[1.28;2.15]	1.27	[0.97;1.67]
Cluster No 3	1.53	[1.17;2.01]	1.25	[0.94;1.66]
Asthma attacks				
Cluster No 1	1.00	-	1.00	-
Cluster No 2	1.60	[1.33;1.93]	1.51	[1.24;1.84]
Cluster No 3	1.80	[1.48;2.18]	1.72	[1.55;1.91]
Asthma-COPD overlap syndrome				
Cluster No 1	1.00	-	1.00	-
Cluster No 2	1.72	[1.40;2.10]	1.59	[1.28;1.98]
Cluster No 3	2.02	[1.64;2.49]	2.05	[1.83;2.29]
Late asthma-onset phenotype				
Cluster No 1	1.00	-	1.00	-
Cluster No 2	1.27	[1.07;1.53]	1.41	[1.15;1.72]
Cluster No 3	1.52	[1.25;1.85]	1.29	[1.15;1.44]

* Model adjusted on asthma treatment level (proxy of asthma severity)

Table S3. Associations between groups identified by latent class analysis and asthma characteristics according to asthma activity. a) Cluster No 1, women with few other drug classes than those for asthma and clinical/environmental factors related to asthma, labeled "Few comorbity-related medications" (45.1% and 61.8% of women with current asthma and past asthma, respectively); b) Cluster No 2, women taking drug classes for allergy, nose diseases, rheumatism /inflammation, pain, infections, bowel diseases and hormonal disturbances, labeled "Predominant allergy-related medications" (28.6% and 23.2% of women with current asthma and past asthma, respectively); and c) Cluster No 3, women more often obese with obstructive sleep apnea syndrome and taking drug classes for gastro-oesophageal diseases, rheumatism/inflammation, pain, bowel diseases, psychological disturbances, cardiovascular diseases, diabetes and dyslipidemia, labeled "Predominant cardiovascular-related medications" (26.3% and 15.0% of women with current asthma and past asthma, respectively).

Outcomes	Women with current asthma (n = 3,023)		Women with past asthma (n = 1,035)	
	OR	[CI95%]	OR	[CI95%]
Uncontrolled asthma				
Cluster No 1	1,00	-	1,00	-
Cluster No 2	1,39	[1,06;1,81]	0,21	[0,01;4,79]
Cluster No 3	1,95	[1,50;2,54]	0,33	[0,02;5,85]
Asthma exacerbations				
Cluster No 1	1,00	-	1,00	-
Cluster No 2	1,50	[1,14;1,98]	0,76	[0,24;2,41]
Cluster No 3	1,31	[0,98;1,75]	1,12	[0,37;3,42]
Asthma attacks				
Cluster No 1	1,00	-	-	-
Cluster No 2	1,32	[1,08;1,62]	-	-
Cluster No 3	1,30	[1,06;1,60]	-	-
Asthma severity				
Cluster No 1	1,00	-	1,00	-
Cluster No 2	3,50	[2,70;4,52]	4,11	[1,89;8,94]
Cluster No 3	2,70	[2,06;3,53]	5,00	[2,18;11,47]
Asthma-COPD overlap syndrome				
Cluster No 1	1,00	-	1,00	-
Cluster No 2	1,47	[1,17;1,83]	1,97	[1,18;3,29]
Cluster No 3	1,62	[1,29;2,03]	2,57	[1,48;4,48]
Late asthma-onset phenotype				
Cluster No 1	1,00	-	1,00	-
Cluster No 2	1,29	[1,04;1,61]	1,04	[0,76;1,41]
Cluster No 3	1,41	[1,12;1,79]	1,35	[0,91;1,99]

CHAPTER V

GENERAL DISCUSSION

I. RESULT SUMMARY

In the context of the worldwide burden of asthma, this thesis in pharmacoepidemiology focused on asthma therapeutic management in real life, addressing the long-term benefits of ICS, the relevance of drug administrative databases as asthma quality of care markers, and the associations between comorbidity-related medications and asthma characteristics.

Our findings mainly relying on the elderly with asthma, a phenotype of particular interest in the context of population ageing and multimorbidity, extended the relevance of the controller-to-total asthma medication ratio as quality of care marker in elderly women with ever asthma. Using a longitudinal approach, we further identified specific patterns of the ratio fluctuations, which were associated with poor asthma-related outcomes. In addition, we suggested a new approach to decipher the complexity of medication use in this specific population, by building the "Pharmacome". Applying a clustering method on drug use among participants with asthma, we identified three clusters of individuals characterized by their medication profiles, which were associated with different risk levels for subsequent poor asthma characteristics. Finally, we failed to demonstrate statistical significant effects of long-term ICS exposure on asthma-related outcomes in adults with persistent asthma, but we observed a trend for benefits of long-term ICS exposure on lung function evolution.

II. DISCUSSION

The discussion focuses on epidemiological, clinical and methodological aspects of this thesis.

A. Epidemiological and clinical aspects

1. Characterizing asthma treatments: adherence, level of maintenance therapy and quality of care

Medication adherence is challenging for patients, especially in chronic diseases (161). According to the World Health Organization, approximately 50% of patients take their medications as prescribed. In the EGEA study, we showed that only 28.2% of young adults with persistent asthma reported ICS regular exposure over time (i.e., at least 6 months per year over a 12-year period on average). In addition, we estimated medication adherence from a comprehensive drug administrative database in the elderly and found that only 24.8% of women with symptomatic asthma were regularly exposed to ICS and/or LTRA over the past two years (i.e., at least four reimbursements of unit per year). The results of this thesis, in which the study of asthma medication adherence was not a primary objective, do not allow any firm conclusion of this public health issue, but are in line with the burden of non-adherence in asthma whatever the population age. Asthma medication adherence is difficult to estimate given its different definitions and assessments across studies (198). Despite a good therapeutic adherence, an inappropriate use of inhalers has been regularly reported in asthma treatment, and may significantly decrease drug efficiency (162). Furthermore, adherence to ICS is a fluctuant process, which varies over time and changes particularly before and after an asthma exacerbation (199, 200).

We estimated the level of asthma maintenance therapy from drug administrative databases among elderly women with current asthma. We showed that 61.7% of them had a high level of asthma maintenance therapy (i.e., steps 4 and 5 according to the GINA classification), suggesting a high proportion of participants with severe asthma and potentially some overtreated participants. Although drug administrative databases provide a useful tool to accurately estimate exposure to asthma treatments, some limitations have to be kept in mind, such as the use of asthma-related medications for other indications than asthma.

We studied the relevance of quality of care markers using drug administrative databases among elderly women from a French healthcare insurance plan. We chose a simple unweighted ratio as a proxy of quality of care, defined as the controller-to-total asthma medication ratio (121). Our findings confirmed the predictive ability of this ratio in our elderly population with current asthma but also in the population with ever asthma, with a 0.5-threshold ratio already used in younger population studies. This suggests the applicability of a simple ratio at population level to prevent poor asthma-related outcomes. We found that the relevance of this ratio was weaker among women with ACOS than among other women, suggesting that the phenotypic heterogeneity impacts the predictive ability of the ratio. This finding may be explained by the different therapeutic strategies recommended according to the syndromic assessment in ACOS (4). Further investigations should be conducted to assess the relevance of the controller-to-total asthma medication ratio among patients with ACOS.

2. Addressing the complexity of asthma from a pharmacoepidemiological viewpoint

We applied an integrative approach to address the complexity of asthma disease from a new viewpoint based on a drug administrative database. Our “Pharmacome” in asthma, built from a scale-free powerful interactive network analysis tool, mapped the undirected and

weighted interconnectivity of medications in order to better understand the complex interplay between conditions. However, the direction of these associations and the biological mechanisms behind these associations remain unclear; whether current asthma leads to comorbidities onset or impairment and so to polymedication, or whether active comorbidities have an impact on asthma clinical expression needs to be further studied. Network models, such as genetic interaction networks or physical interaction networks, have already been constructed to study complex diseases, but, to our knowledge, no model have been built with medications (185, 201, 202). We added a new layer to the previous networks by providing a comprehensive overview of therapeutic management in the elderly. An important challenge now is to establish the relationship between the different levels of networks (i.e., genome, proteome, metabolome, comorbodime, pharmacome, and environment).

3. Unravelling asthma phenotypic heterogeneity using a pharmaco-epidemiological approach

Not considering asthma heterogeneity may mask drug effects in pharmacoepidemiology studies. This is a potential weakness of our study that aimed at assessing the long-term benefits of ICS in young adults with persistent asthma. Previous studies used agnostic methods to identify subjects' clusters according to phenotypic and biological characteristics in asthma, but none considered treatments in a comprehensive way. We used two complementary approaches using a clustering method relying on medication use, estimated from drug administrative data, in the elderly to identify groups of women with different risk levels of poor asthma-related outcomes; the first one relying on the longitudinal data, which identified asthma with specific profiles of the ratio fluctuations, and the second one relying on treatment use, which identified specific profiles of comorbidities. Noteworthy, both approaches led to the identification of profiles statistically associated with subsequent

uncontrolled asthma. In conclusion, our innovative approach adds relevant information of clinical and public health interests. We provide new insights to prospectively consider drug administrative databases to identify patients at risk for uncontrolled asthma.

B. Methodological aspects in pharmacoepidemiology

Through the different methods used (i.e., propensity score method, latent class analysis, network graph vizualization and multiple imputation), this thesis highlights two interesting points on methodological aspects in pharmacoepidemiology research.

1. Propensity score method and indication bias: myth or reality?

The association evaluation validity between drug exposure and diseases depends mainly on the ability to avoid or minimize the indication bias associated with classification errors. In this thesis, we applied the propensity score method in the attempt to avoid the indication bias in the assessment of ICS long-term effects in asthma. Our findings suggest the presence of residual confounding, unmeasured or unknown, inherent to observational studies, and may be explained by a high variation of disease clinical expression over time. In our study, applying such method might highlight its limits, but the propensity score method provides some relevant advantages. Contrary to conventional statistical models, the propensity score method does not take into account the number of events that occurred in the study population but the number of subjects exposed to build the model, allowing to include a larger number of variables (203, 204). In our study, this a priori benefit was limited because the number of subjects exposed to ICS was relatively small (n = 85). The propensity score method appears to provide less biased, more robust and accurate estimates than conventional statistical methods when the studied event is rare (less than 8-10 events per covariates). In our study, controlled asthma was uncommon (11 events per covariates), which may explain result similarity between the counterfactual approach and the conventional statistical methods.

However, this rule is difficult to apply for quantitative variables, such as lung function evolution and health-related quality of life, as in our study. Some authors suggest that logistic regression could be unsuited to the propensity score modelling, and that more complex statistical methods, such as machine learning, might be performed (205).

2. Clustering methods in pharmacoepidemiology research

In this thesis, we applied latent class analysis to identify subjects' clusters in transversal and longitudinal ways, using a pharmacoepidemiological approach. Clustering method knew a growing interest in the last decade in epidemiology but was sparsely used in pharmacoepidemiology. In one study, an implementation of K-means adapted to longitudinal data analysis was used to describe individual trajectories of exposure to psychotropic drugs during pregnancy (206). The performance of latent class analysis (LCA) has been recently evaluated in comparison with agglomerative hierarchical clustering for pharmacoepidemiology research (207). Both clustering methods provide similar results but LCA might be better to detect extreme deviant behaviour.

C. Strengths and limitations

One of the major strengths of this thesis lies in the complementarity of the EGEA and E3N studies. The EGEA study provides a detailed phenotypic characterization of subjects with asthma from validated and standardized questionnaires but also clinical and biological examinations, including lung function testing and genetic data in the two first surveys (EGEA1 and 2). Although specific information was collected at each survey, relatively few data was available on short- and long-term exposure to asthma treatments collected by questionnaire. The agreement between self-reporting and health insurance claims on medication use is substantial in the general population, but self-reporting may be affected by measurement error due to recall bias or the social desirability effect (208). The future

opportunities for accessing to claims data for research in France make the EGEA study a valuable data source for pharmacoepidemiological research in asthma. Such detailed data collected in the EGEA study may not be collected among large populations. The moderate size of the EGEA population limited our statistical power of our analyses but allowed to observe some trends of associations between the long-term exposure to ICS and asthma-related outcomes. The EGEA population is not representative of the general population, especially because asthmatic cases were recruited in chest clinics and may therefore over-represent severe asthma, compared to the general population.

The E3N study includes more than 4,000 women with ever asthma followed for 20 years. Data on both general and respiratory health are coupled with medication reimbursement data from 2004 onwards. Reimbursement data has little been used in France to estimate the quality of asthma therapeutic management at the population level, and never specifically in adults aged over 40 years at inclusion and followed for more than 20 years. Medication dispensation might not accurately reflect drug intake because of poor adherence and technique of medication inhalation (2, 58, 59, 64, 84). However, this potential limitation is substantially mitigated in our population mainly composed of old women with a high educational level and covered by a national insurance plan (84). The homogeneity of the E3N population on different characteristics, such as age, body mass index, smoking status and level of education, may limit conclusions of some subgroups analyses. Nevertheless, such a population allows to limit the biases due to residual confounding factors in our analyses. Focused on respiratory health, the Asthma-E3N study provides no objective measure on respiratory health, especially lung function and bronchial hyperresponsiveness, to confirm asthma status. Nevertheless, the use of standardized and validated questions already used in international studies and repeated over time may limit misdiagnosis. Although the differential diagnosis between asthma and COPD by a self-questionnaire has been validated among health

professionals, those results cannot be directly extended to any other population, even in highly educated elderly population like ours (175). The Asthma-E3N study including a homogeneous population (elderly women belonging to a specific national health insurance plan) limits the generalization of our results, especially to men. Nevertheless, asthma in elderly women is relevant for public health since prevalence and severity of asthma is higher among women compared to men (64). Overall, the E3N study is a particularly relevant population to study the burden of multimorbidity.

III. PUBLIC HEALTH AND CLINICAL IMPACTS

Our findings are of interest both in public health and clinical viewpoints. In line with the development of the pharmacoepidemiological surveillance based on medico-administrative databases, our findings allow to identify and ultimately provide clues for the care of the elderly with asthma and new insights to assess asthma therapeutic management over time. Relying on the "Pharmacome" in asthma, we assessed the impact of comorbidity-related medications on asthma and identified high-risk profiles for poor controlled asthma. From a clinical perspective, our findings provide a better understanding of asthma comorbidities in the elderly. These results may be integrated into "4P medicine", allowing healthcare professionals to enhance and personalize patients' care (99).

Our findings are of particular importance in the policies on ageing. Health and care services are undergoing changes to adapt systems to the growing demands caused by expansion of chronic diseases and ageing. In Europe, the European Commission launched the European Innovation Partnership on Active and Healthy Ageing to enhance European Union competitiveness and tackle societal challenges through research and innovation (209). The initiative AIRWAYS ICPs (Integrated care pathways for airway diseases) (210, 211) was approved by the European Innovation Partnership on Active and Healthy Ageing as the model

of chronic diseases to launch collaboration to develop practical multisectoral care pathways to reduce chronic respiratory disease burden, mortality and multimorbidity (212). The information obtained from this thesis will be of importance on the action plan development on chronic respiratory disease in the elderly. From this thesis, decision-makers may appreciate the unique opportunity of pharmacoepidemiological studies to improve the performance of their healthcare systems and population health. Our findings could also participate in improving asthma therapeutic management and thus lead to medical and economic benefits.

IV. PERSPECTIVES

This thesis in pharmacoepidemiology of asthma opens new perspectives, including perspectives in multimorbidity, pharmacoeconomy and epigenetics.

A. Asthma: an example of chronic disease

We used asthma as a model of complex chronic disease. Chronic respiratory diseases share common environmental risk factors (e.g., tobacco, nutrition, sedentary lifestyle) with other non-communicable diseases, leading to sustained local and systemic inflammation and impaired ageing (213). Active and healthy ageing is a major societal challenge shared by all countries. Applying the pharmacoepidemiological approach used in this thesis to other chronic diseases in large populations is relevant to enhance our knowledge in the context of multimorbidity. Moreover, characterizing trajectories of medication use from drug administrative databases will help us to better understand the dynamic process of multimorbidity over time. The E4N study, that recruited the family members of E3N women (fathers of their children, children and grandchildren) will provide a wide age-range population covering, but not limited to, the elderly, with relevant source of data to study

multimorbidity in France. Further studies combining claims data and detailed characteristics of large populations are also needed.

B. Asthma therapeutic management: healthcare systems and economic burden

This thesis focused on asthma therapeutic management in France, particularly in the elderly. Asthma burden differs significantly between the endo-phenotypes themselves but also between national healthcare systems. According to the World Health Organization, the performance of healthcare systems fluctuates significantly between countries, even among countries with comparable income levels and health spending. It is therefore essential to replicate our findings in other populations with asthma. Moreover, this thesis confirms that a large part of adults and old women with asthma does not have an optimal therapeutic management, leading to substantial additional costs. In 2010, asthma treatments represented respectively 32.3% and 71.8% of the total and direct asthma costs in France, with a significant variation of their economic burden according to asthma control level and age (30). A pharmaco-economic study on cost evolution associated with asthma would be of particular relevance in the elderly. Furthermore, applying a comprehensive approach integrating all medications in a pharmaco-economic study would be helpful to comprehensively characterize therapeutic costs according to multimorbidity profiles.

C. Deciphering the therapeutic complexity and heterogeneity of asthma: what are the underlying mechanisms?

We provide a new viewpoint using a pharmacoepidemiological approach to decipher asthma complexity and heterogeneity. However, given the singularity of our study population, further studies are needed to confirm our findings. The subjects' profiles identified in this

thesis integrate biological and clinical characteristics, from molecules to the environment. Beyond environmental factors and genetic polymorphisms, epigenetic regulation has recently emerged as a potential mechanism that could explain the differences observed in medication drug response across individuals (214, 215). For example, corticosteroids exert their antiinflammatory effects by inducing acetylation of antiinflammatory genes and by recruiting histone deacetylase-2 (HDAC2) (216). The reduced activity or expression of HDAC2 led to a corticosteroid resistance. Low concentration of theophylline reverses corticosteroid resistance by restoring HDAC2 activity and directly inhibites oxidant-activated PI3Kdelta (216). Other epigenetic mechanisms, such as the regulation of FoxP3 by DNA methyltransferase inhibitors, which may modulate the airway inflammation, may affect gene expression implied in asthma (217). A better understanding of these epigenetic mechanisms is needed. The E3N and EGEA studies, that have epigenetic programs in progress through the methylome, should offer new pharmaco-epigenetics opportunities.

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