Impact of a population-based asthma management program in France (Sophia Asthme): A matched controlled before-and-after quasi-experimental study using the French health insurance database (SNDS)

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TITLE PAGE

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ABSTRACT

Background: *Sophia Asthme* (SA) is a chronic disease management program of the French national health insurance for adult patients with asthma. We evaluated the early impact of this intervention.

Methods: We conducted a matched controlled, before-and-after quasi-experimental study within the French Health Insurance Database (SNDS). The SA program was implemented in a set of 18 *Départements* in France and targeted 18-to 44-year-old subjects, with at least two reimbursement dates for asthma drug therapy during the 12-month period prior to program targeting. Change in outcomes was assessed from the "before program" period (January-December 2014) to the "after program implementation" period (Mars 2015–February 2016) in the program group (eligible to SA program in the 18 *Départements*) and in the matched controlled group. The main outcome measure was the before-after change in proportion of subjects with a controllers/(controllers+relievers) ratio >50%.

Findings: Of the 99,578 subjects of the program group, 9,225 (9·3%) actually participated in SA program. The program had no significant impact on the proportion of subjects with a ratio>50%. However, subjects exposed to SA program were significantly more likely to be dispensed controller medications (OR=1·04; 95% CI, 1·01 to 1·07), and to sustain their use of these medications (OR = 1·08; 95% CI, 1·05 to 1·12).

Interpretation: We did not demonstrate any significant impact of the program on the primary outcome. The modest yet encouraging findings of this early evaluation suggest the need for reformulation of the program and its evaluation.

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INTRODUCTION

Despite the availability of highly effective therapies, achieving asthma control remains tremendously challenging, mostly because of inappropriate use of asthma controller medications. [1] Poor asthma control is responsible for acute exacerbations, which can lead to emergency visits, hospitalizations, and even premature deaths. With an estimated global asthma prevalence among adults ranging from 1% to 21% [2] and 383,000 related deaths in 2015, [3] asthma places substantial burdens on the patients, healthcare system and society; [4,5] it is a major public health problem recognized by the World Health Organization (WHO).[3]

Various programs have been implemented worldwide to improve asthma control.[6] *Sophia Asthme* (SA) program is a chronic disease management program developed by the National French Insurance Service (*Caisse Nationale de l'Assurance Maladie* (CNAM)). It aims to enhance self-management and induce behavior changes, at a sustainable cost to the CNAM budget.

Sophia program was first developed for diabetic patients in 2008, and included a free web site, written information and telephonic nurse intervention. Recently, a pilot program was developed for asthma patients, aiming at improving asthma control. The objective of this study commissioned by the CNAM was to assess the early effect of the pilot phase of the SA program on asthma outcomes in adult asthma patients.

METHODS

Description of the intervention

As a health insurer, the CNAM defines and implements risk-management actions. In this framework, the CNAM launched the pilot experiment of SA program [7] in January 2015, in 18 among 96 *Départements* of mainland France *(Alpes-Maritimes, Ariège, Côte-d'Or, Haute-Garonne, Gers, Gironde, Hérault, Loire, Loiret, Marne, Meurthe-et-Moselle, Nord, Puy-de-Dôme, Hautes-Pyrénées, Sarthe, Somme, Tarn, and Seine-Saint-Denis)*. Targeting the 18- to 44-year-old asthmatic patients, SA program consists primarily of a nurse-delivered, phone-based intervention. Every individual identified in the CNAM claims databases and meeting the selection criteria was invited to take part in the program. The program participants (as opposed to "program non-participants") started receiving phone calls after mail or online registration made by the patient or their general practitioner (GP).

During the first phone call, medical data (asthma control during the last 4 weeks according to Global Initiative for Asthma (GINA) criteria[8], smoking status and physical exercise practice) were collected. During the following calls, specialized nurses trained in behavioral counseling conducted motivational interviews to promote positive attitudes towards asthma, using a computer-assisted telephone system. Telephone calling periodicity was determined initially and updated afterwards according to a set of criteria reflecting asthma control. After the first phone call, a bimonthly call was planned for patients who had had a hospitalization or ER visit for asthma and for those who had poor symptom control according to GINA criteria. An annual call was planned otherwise. Hospitalization and ER visits for asthma were monitored in real-time (from claims/hospital discharge data) for all program participants, so that patients could benefit from additional calls in the event where asthma hospitalization or

ER visit occurred since the last phone call. The same criteria were applied after the second call to determine the periodicity of the subsequent calls. These criteria encompassed both asthma control and medical use from the SNDS database. The content of counseling was recorded in a dedicated software, and tailored for each program participant based on its personal situation (lifestyle, state of health and medical care, social and family environment). Nurses offered appropriate advice and information, in order to promote a greater understanding of the relation between medication adherence and asthma control. They urged patients to seek medical aid and drug treatment, when appropriate.

Participants without any telephone call during the intervention period were classified as participants with “low–intensity intervention”, those who had one to three and more than three calls as participants with “moderate-intensity and “high-intensity intervention”, respectively.

Besides telephone calls, all program participants received printed material developed by health care professionals and validated by a scientific committee. The material included three leaflets and bi-monthly e-newsletters on asthma. The CNAM also provided unrestricted access to a dedicated website. The written material and the website included information on prevention of exacerbations, smoking cessation, physical activity and management of the disease.

Population

Subjects for the pilot experiment were identified and followed-up within the French Health Insurance database (*Système National Des Données de Santé- SNDS*). Eligibility criteria for the SA program were the following: 1) being aged 18 to 44 years; 2) having at least two different reimbursement dates for asthma medications (R03 codes according to the

Anatomical Therapeutic and Chemical (ATC) classification system) in the last 12 months; 3) being covered by the general health insurance scheme; 4) being affiliated with a local healthcare insurance office (*Caisse Primaire d'Assurance Maladie* – CPAM) attached to any of the 18 aforementioned *Département*s for at least 12 months before program deployment; and 5) having a GP also affiliated with a CPAM attached to any of the 18 aforementioned *Départements* for at least 12 months before program deployment.

The study population involved all subjects eligible to SA program from *Départements* with the program (i.e., the exposed) matched on a propensity score and stratification variables, with subjects eligible to SA program except they and their GP were affiliated with a CPAM of mainland *Départements* not covered by the program (i.e., the unexposed).

The geographical areas chosen for the pilot experiment cover a population of approximately 168,000 subjects meeting the aforementioned eligibility criteria. This population was not chosen to be strictly representative of all asthmatic patients in France.

Study design

This evaluation study was designed as a prospective, non-randomized, matched controlled, quasi-experimental before-and-after study. [9] We defined three periods: (i) 1 January 2014 – 31 December 2014: the 12-month "before program implementation" period, (ii) 1 January 2015 – 28 February 2015: the implementation period, and (iii) 1 March 2015 – 29 February 2016: the 12-month "after program implementation" period. The exposed group (intervention group) was composed of individuals targeted by SA program. The unexposed group was composed of matched individuals meeting eligibility criteria of the intervention group except they and their GP were affiliated with CPAM of mainland *Départements* not covered by the program. Each subject from the intervention group was matched with an

unexposed, by stratification variables (asthma-related hospital stay in the last 12 months (yes *vs*. no), the number of asthma drug deliveries in the last 12 months (2 *vs*. ≥3) and age at program enrollment (< 40 *vs.* ≥ 40)), and by the propensity score of being exposed.[10–12] We report our findings in accordance with The Reporting Quality of Non Randomized Evaluations of Behavioral and Public Health Interventions (TREND) statement. [13]

Outcome measures

The outcomes were extracted from the SNDS database in 2015 and match the desired effects of the intervention: improved asthma control, improved adherence to controller asthma medications, improved use of healthcare resources, reduced exacerbations and days off work.

The primary outcome of interest relied on an asthma medication ratio measuring the proportion of controllers out of total asthma therapy (i.e., controllers and relievers) over a given study period. [14] More precisely, it is the ratio of inhaled corticosteroid (ICS) (whether in fixed combination with long-acting β-agonists (LABAs) or not) plus leukotriene receptor antagonist (LTRA) to total asthma medications (R03 according to ATC classification, Appendix 1). In this study, the primary outcome was a high ICS+LTRA/R03 ratio (i.e., ≥ 50%), which has been shown in claims data to be associated with fewer asthma-related hospitalizations, fewer emergency room (ER) visits,[14] and better patient-centered asthma outcomes (such as asthma quality of life and symptoms severity).[15] The secondary outcomes included asthma exacerbations (defined as asthma-related hospitalization, asthma –related ER visit or visit to the GP with a dispensation of systemic corticosteroids within seven days of the GP visit), urgent care visits (asthma-related ER room visits and hospitalizations, GP visits for asthma exacerbations), routine asthma visits (GP visits for asthma- defined as dispensation of R03 drugs within seven days of the GP visit-, pulmonologist visits, and pulmonary function

testing), dispensation of at least one controller medication, dispensation of four or more SABA, sustained use of controller medications (defined as five or more dispensations of ICS - in fixed association with LABA or not- or eight or more units of LTRA), adherence to asthma controller medication (ICS alone or in fixed combination with LABA) as measured by the Medication Refill Adherence (MRA), [16] and work absenteeism as measured by the number of sick leave days related to asthma (Appendix 2).

Data sources

This study was undertaken using a database formed by linking the SNDS [17] database and SA program database, which only included the program participants (questionnaire administered upon entry into the study, and program operational data).

In France, the SNDS compiles data from the French National Health Insurance System (including the national hospital-discharge summaries database system - PMSI).[18] Information on healthcare reimbursement, ambulatory and hospital expenditures data, as well as socio-demographics including age, gender, French administrative area of residence, advantage of the Complementary Universal Health Coverage (CMU-C, an individual measure of low socio-economic position (SEP)), and long-term chronic disease status allowing for full medical reimbursement, is available in the SNDS. Data obtained for subjects included in our study comprise sociodemographic and outpatient reimbursed health visits and drugs (coded with ATC classification) on the one hand, and the dates of start and end of hospital stays, with diagnostic codes (primary, related and associated diagnoses coded with the International Information Classification of Diseases, version ICD-10), [19] and most of costly procedures (*Classification commune des actes médicaux,* CCAM),[20] on the other hand. The study funder and commissioner (National Health Insurance Fund) undertook the linkage between SNDS records and the information collected within SA program. According to the

law (n°2016-41, JORF 2016), a permanent access to SNDS is granted to CNAM employees, but also to subcontractor acting under the authority of CNAM, under very strict conditions (accreditations, secure access…). The statistician authors, as subcontractors to CNAM, had complete and free access to the database. This evaluation is covered by the law of the 6th January 1978 and the decree n ° 2012-1249 of the 9th November 2012 authorizing the creation of personal data processing for the implementation of health prevention and support programs for insured persons. The data processing was the subject of a commitment of conformity to the aforementioned decree.

Power calculation

The a priori power calculation was based on a 5 % increase in the proportion of patients with a ratio ICS+LTRA/R03 ≥ 50% among program participants and their matched unexposed subjects in the intervention group. Assuming 160,000 subjects in the exposed group and a rate of 10% of program participation, we reached a power of 80% with a 5% two-tailed test.

Statistical methods

We generated a propensity score with all the subjects, for matching subjects of the intervention (exposed) and unexposed groups within each stratum (caliper=0·20). The probability of being exposed to the program was modeled using a multivariate logistic regression including the following covariates: age, sex, average number of units of the ATC R03 class delivered over the years 2012, 2013 and 2014, CMU-C, prevalence of asthma in the area of residence, as well as characteristics of the geographic location of GP practice (Rey deprivation index, [21] which is an area-level measure of SEP, the medical density, the size, and the rural or urban character). [22] The prevalence of asthma reflects in an integrated and pragmatic way the factors that trigger asthma exacerbations (such as atmospheric

conditions, weather conditions, pollination, influenza, etc.); it was derived from a national survey of adults in France (*Enquête santé protection sociale -ESPS)*[23] and a national school health survey.[24,25] We used standardized mean differences and histograms, for analyzing balance in measured baseline variables before and after matching. After propensity-score matching, we compared differences in patient's outcomes using the difference-in-differences (DiD) analysis approach. We compared the change in outcomes in subjects of the intervention group between the "before program implementation" period and the "after program implementation" period with the change of outcomes in subjects of the unexposed group within the same time period, by use of linear mixed models and generalized mixed models for testing the effect of the program on continuous and dichotomous outcomes, respectively.

We conducted subgroup analyses to focus on populations in which the probability to be asthmatic was higher than in the whole study population: (i) patients with at least three different reimbursement dates of R03 in 2013 (*a priori* subgroup analysis), (ii) patients with at least one reimbursement date of R03 in 2012, and (iii) patients with more stringent criteria for the definition of asthma (algorithm developed by the CNAM: subjects with ≥ 1 IgE antagonist or ≥ 1 xanthine or ≥ 1 LTRA (alone or with ICS) or ≥ 3 ICS-LABA or ≥ 3 ICS or ≥ 3 LABA or ≥ 3 SABA are considered asthmatic).

All analyses were conducted using SAS guide 9.3 (SAS Institute, Cary NC) and R version 3.1.1. R Core Team (2014).[26] A level of a two-tailed statistical significance of $p < 0{\cdot}05$ was used for all statistical tests performed.

RESULTS

Baseline characteristics

In January 2015, 108,053 subjects were targeted by SA program. Of those, 105,957 were eligible to the intervention group of the study (Figure 1). After matching, 199,156 individuals were included in the study, with 99,578 in each group. The quality of propensity matching is graphically displayed in Supplemental Figures S1A and S1B (Appendix 3). Mean age (± SD) was 34 (±7) years (IQR 29-41). Women and CMU-C recipients constituted respectively 60·3% and 19·5% of the study population (Table 1). This population was characterized by features suggesting poor asthma control (less than half of them had an ICS+LTRA/R03 drug ratio ≥0·5, one third of them exhibited at least one asthma exacerbation during the previous year) and little adherence to treatment (7·1% had a MRA >80%)) (Table 2). A small proportion (11%) of them consulted a lung specialist and about a half received ICS (alone or in combination with LABA) during the year preceding the program.

Description of *Sophia Asthme* program outputs

In the intervention group, 9,225 (9·3%) subjects actually participated in the program. Mean number telephone calls was 1·8. Fifty-four percent of the participants had “low-intensity intervention”; 30·4 % and 15·6 % had “moderate-intensity” and “high-intensity intervention”, respectively.

The written support provided was the same for all participants, but only those who communicated their e-mail address (58·8%) received the e-newsletters. Among them, the majority received four or five e-newsletters (18·9 % and 31·8 % of the participants, respectively). The majority of the participants (80·6%) received three leaflets; 16·2 % received two leaflets.

Effects of *Sophia Asthme* program

Table 2 presents the evolution of outcomes before and after program implementation. Most indicators decreased over time in both the intervention and the unexposed group, indicating a period effect. From the “before program implementation” period to the “after program implementation” period, the proportion of subjects with a high ICS+LTRA/R03 decreased in both groups by 4·9 %. No significant difference was observed for other asthma control or for medication adherence indicators. However, the effect of SA program was significant in terms of more frequent patients with at least one controller medication prescription dispensed (OR = 1·04; 95% CI, 1·01 to 1·07), with sustained use of controller medications (OR = 1·08; 95% CI, 1·05 to 1·12), and with higher total number of R03 prescriptions dispensed (β = 0·36; 95% CI, 0·25 to 0·47) in the intervention group..

Subgroup analyses

The results were similar for patients with three or more R03 prescriptions dispensed in the last 12 months prior to program targeting (in 2013), but the program effect size was relatively larger on the total number of R03 prescriptions dispensed (β = 0·51; 95% CI, 0·35 to 0·67). The comparison of program participants to their matched unexposed showed larger effects sizes on the sustained use of controller medications (OR = 1·29; 95% CI, 1·16 to 1·43) and on the total number of R03 prescriptions dispensed (β = 0·76; 95% CI, 0·36to 1·16). In addition, this subgroup analysis revealed a significant protective effect of the program on the risk of asthma exacerbations (OR = 0·90; 95% CI, 0·83to 0·99) and a significant decrease in the number of asthma-related sickleave days (β =-0·33; 95% CI, -0·59 to -0·07) (Table 2). Results were similar in the people with asthma according to the CNAM algorithm (Table 3).

DISCUSSION

In this paper, we have examined the early impact of an asthma disease management program in France, SA. The study did not achieve its primary objective, which was to demonstrate an increase in the proportion of patients with a high ICS+LTRA/R03 ratio in the intervention group. Additionally, there was no evidence that the program reduced the risk of asthma-related hospitalizations, ER visits for acute asthma, and asthma exacerbations. However, the program was found to be associated with an increase in the dispensation of R03, the proportion of subjects with dispensation of at least one controller medication, and the sustained use of controller medications. Furthermore, in subgroup analyses focusing on people more likely to be asthmatic, the impact of the program was significant for some asthma treatment-related outcomes (R03 prescriptions dispensed, at least one controller medication prescription dispensed, sustained use of controller medications), and some clinical outcomes (asthma exacerbations, number of asthma-related sickleave days).

These results can be interpreted as an absence of impact of the SA program. However, alternative explanations must be discussed. First, the (two months') duration of the implementation period was not sufficiently long to translate into better asthma outcomes. Chronic conditions require long-lasting interventions to promote health behavior changes, such as motivation for medication adherence, smoking cessation, and risk reduction strategies (avoidance of triggers and pollutants). Clinical changes may have occurred outside the timeframe of the observation period. There was an improvement in the use of controller medications (which is a process indicator), we would therefore expect a decrease in asthma exacerbation over a longer time span. Second, the study was underpowered. The initial power calculation was based on the best available data, and suggested that 160 000 patients targeted by the program with a participation rate of 10% would give 80 % power to detect a

311 5 % increase in the primary outcome among SA participants. Unfortunately, the number of
312 individual eligible to the program and the participation rate were smaller than anticipated.
313 The low uptake of the intervention may be due to early assessment (some people may have
314 started to participate after the implementation period). It could also be due to suboptimal
315 targeting of patients diagnosed with asthma: the algorithm used to target the population (at
316 least two deliveries of R03 over the last 12 months) was probably not specific enough,
317 stressing the need for a more specific targeting of the SA program. Third, the population was
318 mainly of low severity asthma, with only 3.7% with LTD status for severe asthma, and 0.36%
319 with an asthma-related hospitalization in 2014. Thus the room for improvement on severe
320 outcomes as hospitalization was very small. Hence, we performed a priori and post-hoc sub-
321 group analysis, so that the captured population better matches the population of interest.
322 These analysis generated results congruent with the primary analysis, but relatively larger
323 and significant positive effects were observed for some of the secondary treatment-related
324 and clinically relevant outcomes (including asthma exacerbations and sickleave days).
325 Fourth, the participation rate to the SA program was low at this early evaluation, inducing a
326 dilution effect. Fifth, we cannot exclude that the program lacked of a component primarily
327 targeting healthcare professionals (*e.g.*, physician education and training). The use of written
328 personalized action-plan for self-management support may also have been missing.
329 According to the literature, even in countries that have been proactive about recommending
330 asthma self-management, three quarters of asthmatic patients are not provided with
331 written action plans.[27,28] Finally, our findings are consistent with the literature indicating
332 overall small effects and no effect on ER visits. [6,29]
333 Major strengths of this study include the use of routinely collected health data and the large
334 number of geographical areas involved, allowing a very good external validity of the results;

the large sample size, enabling precise effect size estimates; and the relevance of outcomes assessed. In particular, effects on asthma exacerbations and days off work are typically insufficiently reported in studies evaluating asthma management programs, according to the Cochrane systematic review published recently by Peytremann-Bridevaux and colleagues. [27] Keeping in line with their recommendations, we assessed process of care indicators (*e.g.*, MRA rate for controller medications, dispensation of controller medications) and healthcare utilization indicators (*e.g.*, routine GP visits, ER visits) to better interpret the outcomes results at the patient-level.

However, some limitations should be considered when interpreting the results of this study. First, the design of the evaluation was performed after the implementation perimeter was planned by the CNAM means that it was not possible to randomly assign patients to the intervention and control groups nor to promote a more focused target population. We used, as recommended in such cases, [30] a controlled before-and-after quasi-experimental design with matching on stratification variables and propensity score. Quasi-experimental studies (where individuals are not randomly allocated)[30] include some attempt to limit or control threats to internal validity but we cannot exclude the possibility of a residual confounding bias Second, in healthcare databases, outcomes are usually addressed by use of proxies, which can induce measurement errors. However, we used proxies similar to those used in other studies, and, by design, these measurement errors are not differential, thus can only bias towards the null. Third, as stated above, the study was underpowered. The *a posteriori* power (keeping the initial assumptions) in the light of observed numbers is of 52% to detect a difference of 5% among the program participants and matched unexposed people (corresponding to a difference of 0.4 % for the whole study population). Here we had a power of 80% to detect in the program participants a difference of 7% (0.6% for the whole study population)

CONCLUSION

In conclusion, SA program piloting phase was not associated with a significant effect at this early phase evaluation on the primary outcome, the ICS+LTRA/R03 ratio. It had a modest impact on some secondary outcomes, particularly on specific subgroups of patients more likely to be asthmatic, leaving open the possibility that suboptimal targeting of the population undermined the evaluation of the program effectiveness.

Our results can help the CNAM making informed decisions about whether and how to continue to support this program, by improving the targeting of the population and considering reformulation of the program followed by a subsequent evaluation.

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TABLES

Table 1. Characteristics of the included subjects during the "before program" period, across groups: *Sophia Asthme Program* intervention (with program participants and non-participants) and matched unexposed groups.

Variables	Intervention (i.e. exposed) group				Unexposed group
	Total	**Program participants**	**Program non-participants**	***P value***	
No. of subjects	99,578	9,226	90,353		99,578
Demographics					
Age (years), mean (SD)	34·40 (7·25)	35·32 (7·18)	34·30 (7·25)	<0.0001	34·22 (7·45)
Female	60,076 (60·33%)	5,837 (63·27%)	54,240 (60·03%)	<0.0001	60,454 (60·71%)
CMU-C* recipient	19,366 (19·45%)	1,968 (21·33%)	17,398 (19·26%)	<0.0001	20,819 (20·91%)
Rey deprivation index (unweighted) quintiles of the municipality where the GP is professionally based				<0.0001	
1st quintile	26,828 (26·94%)	2,369 (25·68%)	24,459 (27·07%)		24,474 (24·58%)
2 nd quintile	20,107 (20·19%)	1,847 (20·02%)	18,260 (20·21%)		20,102 (20·19%)
3 rd quintile	14,803 (14·87%)	1,310 (14·20%)	13,493 (14·93%)		14,633 (14·70%)
4 th quintile	14,963 (15·03%)	1,408 (15·26%)	13,556 (15·00%)		15,391 (15·46%)
5 th quintile	22,877 (22·97%)	2,292 (24·84%)	20,585 (22·78%)		24,978 (25·08%)
Geographic location of GP Rural (vs Urban)	10,223 (10·27%)	843 (9·14%)	9,380 (10·38%)	0.0002	10,951 (11·00%)
Clinical					
Long-term chronic disease status for severe asthma in 2014	3,706 (3·72%)	570 (6·18%)	3,136 (3·47%)	<0.0001	6,428 (6·46%)

(or before)					
Asthma-related hospitalization in 2014	355 (0·36%)	82 (0·89%)	273 (0·30%)	<0.0001	355 (0·36%)
No. of R03 medications					
No. of R03 prescription dispensed during the "before program implementation" period, mean (SD)	4·46 (3·03)	4·87 (3·04)	4·41 (3·02)	<0.0001	6·10 (4·71)
No. of R03 prescriptions dispensed in 2012, mean (SD)	7·74 (6·08)	8·56 (5·94)	7·66 (6·08)	<0.0001	5·39 (5·18)

Data are no. (%) of patients, unless otherwise indicated.
*CMU-C, complementary universal health coverage.

Table 2. Change in outcomes form the "before program implementation" period to the "after program implementation" period: a) for patients in the intervention (i.e. exposed) and unexposed groups, b) for program participants and their matched unexposed

Table 2 a	Intervention (i.e. exposed) group (n=99,578)			Matched Unexposed group (n=99,578)			DiD	OR or slope [a]	*P* value
	Period		Absolute	Period		Absolute			
	"before program"	"after program"	Change	"before program"	"after program"	Change			
Process outcomes									
Indicators of asthma control									
ICS+LTRA/R03≥0.5	47,509 (47·71%)	42,588 (42·77%)	-4·9%	48,949 (49·16%)	44,067 (44·25%)	-4·9%	0·0%	1·00 (0·97;1·03)	0·8303
≥ 4 SABA	19,186 (19·27%)	17,887 (17·96%)	-1·3%	27,402 (27·52%)	25,468 (25·58%)	-1·9%	0·6%	1·02 (0·99;1·06)	0·1790
Controller medication									
At least one controller medication dispensed	61,713 (61·97%)	55,730 (55·97%)	-6%	67,383 (67·67%)	60,998 (61·26%)	-6·4%	0·4%	1·04 (1·01;1·07)	**0·0082**
Sustained use of controller medication [b]	22,674 (22·77%)	21,288 (21·38%)	-1·4%	34,361 (34·51%)	31,614 (31·75%)	-2·8%	1·4%	1·08 (1·05;1·12)	**<0·0001**
Total no. of R03 dispensed, mean (SD)	5·99 (9·02)	5·67 (9·45)	-0·32	9.87 (14·72)	9.19 (14·79)	-0·68	0·36	0·36 (0·25-0·47)	**<0·0001**
Adherence to controller asthma medications									
MRA>80%	7,069 (7·10%)	6,958 (6·99%)	-0·1%	14,407 (14·47%)	13,503 (13·56%)	-0·9%	0·8%	1·10 (1·04;1·16)	**0·0004**

Healthcare utilization outcomes									
Urgent care visits									
At least one asthma-related hospitalization	355 (0·36%)	266 (0·27%)	-0·1%	355 (0·36%)	417 (0·42%)	0·1%	-0·2%	0·54 (0·42;0·69)	**<0·0001**
At least one ER visit for asthma	3,487 (3·50%)	3,101 (3·11%)	-0·4%	4,723 (4·74%)	4,262 (4·28%)	-0·5%	0·1%	0·99 (0·92;1·06)	0·7084
At least one GP visit for asthma exacerbation [c]	32,731 (32·87%)	30,785 (30·92%)	-2%	31,452 (31·59%)	29,943 (30·07%)	-1·5%	-0·4%	0·98 (0·95;1·01)	0·1423
Routine visits									
At least one pulmonologist visit	11,355 (11·40%)	10,867 (10·91%)	-0·5%	11,785 (11·83%)	10,962 (11·01%)	-0·8%	0·3%	1·04 (1·00;1·08)	0·0774
At least one routine asthma GP visit [d]	59,017 (59·27%)	53,728 (53·96%)	-5·3%	63,153 (63·42%)	57,748 (57·99%)	-5·4%	0·1%	1·01 (0·99;1·04)	0·3642
At least one pulmonary function testing	12,075 (12·13%)	11,241 (11·29%)	-0·8%	12,346 (12·40%)	11,391 (11·44%)	-0·1%	0·1%	1·01 (0·97;1·06)	0·5625
Patient level outcomes									
At least one asthma exacerbation [e]	34,303 (34·45%)	32,247 (32·38%)	-2·1%	33,712 (33·85%)	31,930 (32·07%)	-1·8%	-0·3%	0.98 (0.96-1.02)	0·3530
Work absenteeism									
No. of sickleave days related to asthma, mean number (SD), days	0.87 (9·35)	0.76 (8·43)	-0·11	0·90 (9·96)	0.88 (9·58)	-0·02	0·09	0·09 (-0·20;0·03)	0·1360
At least one sickleave episode related to asthma	4,908 (4·93%)	4,613 (4·63%)	-0·3%	4,909 (4·93%)	4,768 (4·79%)	-0·1%	-0·2%	0·97(0·91;1·02)	0·2299
No. of days of sickleave days related to asthma among those who had one or more days of sickleave days related to asthma, mean (SD) *	17,61 (38·46)	16,39 (35·73)	-1·22	18,32 (41·15)	18·43 (39·91)	0·11	-1·33	-	-

Table 2 b	Program participants (n=9,225)			Matched Unexposed group (n=9,225)			DiD	OR or slope [a]	*P* value
	Period		Absolute	Period		Absolute			
	"before program"	"after program"	Change	"before program"	"after program"	Change			
Process outcomes									
Indicators of asthma control									
ICS+LTRA/R03≥0.5	5,312 (57·58%)	5,073 (54·99%)	-2·6%	4,748 (51·47%)	4,393 (47·62%)	-3·8%	1·3%	1·06 (0·97;1·17)	0·1871
≥ 4 SABA	2,230 (24·17%)	2,186 (23·70%)	-0·5%	2,743 (29·73%)	2,563 (27·78%)	-2·0%	1·5%	1·10 (0·99;1·20)	0·0861
Controller medication									
At least one controller medication dispensed	6,945 (75·28%)	6,518 (70·66%)	-4·6%	6,630 (71·87%)	6,046 (65·54%)	-6·3%	1·7%	1·09 (0·98; 1·20)	0·1093
Sustained use of controller medication [b]	2,790 (30·24%)	2,799 (30·34%)	0·1%	3,611 (39·14%)	3,267 (35·41%)	-3·7%	3·8%	1·29 (1·16;1·43)	**<0·0001**
Total no. of R03 dispensed, mean (SD)	7·78 (10·00)	7·84 (11·50)	0·06	10·80 (14·22)	10·10 (15·12)	-0·7	0·76	0·76 (0·36;1·16)	**0·0002**
Adherence to controller asthma medications									
MRA>80%	896 (9·71%)	947 (10·27%)	0·6%	1,518 (16·46%)	1,455 (15·77%)	-0·7%	1·2%	1·17 (1·01;1·36)	**0·0354**
Healthcare utilization outcomes									
Urgent care visits									
At least one asthma-related hospitalization, mean (SD)	82 (0·89%)	47 (0·51%)	-0·4%	82 (0·89%)	58 (0·63%)	-0·3%	-0·1%	0·73 (0·40;1·35)	0·3182
At least one ER visit for asthma	513 (5·56%)	420 (4·55%)	-0·1%	507 (5·50%)	435 (4·72%)	-0·8%	-0·2%	0·95 (0·78;1·15)	0·5882

At least one GP visit for asthma exacerbation [c]	3,408 (36·94%)	3,087 (33·46%)	-3·5%	2,942 (31·89%)	2,828 (30·66%)	-1·2%	-2·2%	0·90 (0·82;0·99)	**0·0229**
Routine visits									
At least one pulmonologist visit	1,685 (18·27%)	2,067 (22·41%)	4·1%	1,181 (12·80%)	1,141 (12·37%)	-0·4%	4·6%	1·41 (1·25;1·59)	**<0·0001**
At least one routine asthma GP visit [d]	6,551 (71·01%)	6,062 (65·71%)	-5·3%	6,122 (66·36%)	5,626 (60·99%)	-5·4%	0·1%	0·99 (0·90;1·08)	0·7870
At least one pulmonary function testing	1,716 (18·60%)	2,091 (22·67%)	4·1%	1,233 (13·37%)	1,186 (12·86%)	-0·5%	4·6%	1·40 (1·25;1·58)	**<0·0001**
Patient level outcomes									
At least one asthma exacerbation [e]	3643 (39·49%)	3267 (35·41%)	-4·1%	3193 (34·61%)	3019 (32·73%)	-1·9%	-2·2%	0·90 (0.83;0·99)	**0·0289**
Work absenteeism									
No. of sickleave days related to asthma, mean number (SD), days	1·21 (10·73)	0·91 (8·78)	-0·30	1·07 (11·31)	1·10 (11·50)	0·03	-0·33	-0·33 (-0·59;-0·07)	**0·0119**
At least one sickleave episode related to asthma	547 (5·93%)	479 (5·19%)	-0·7%	480 (5·20%)	497 (5·39%)	0·2%	-0·9%	0·83 (0·69;0·99)	**0·0463**
No. of days of sickleave days related to asthma among those who had one or more days of sickleave days related to asthma, mean (SD) *	20·39 (39·39)	17·52 (34·57)	-2·87	20·49 (45·41)	20·41 (45·42)	-0·08	-2·79	-	-

Data are no. (%) of patients, unless otherwise indicated. Values in bold indicate significant associations (p<0.05).
DiD, difference-in-differences (change in outcomes in exposed minus change in outcomes in the unexposed: if the DiD is positive, it means the increase in the variable is higher in the exposed vs unexposed); ER, emergency room; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; MRA, medication refill adherence; GP, general practitioner; SABA, short-acting β-agonist; LABA, long-acting β-agonist.
[a] The following equation was used: $Yi=\beta0 + \beta1\ INTERVENTION + \beta2\ PERIOD + \beta3\ (INTERVENTION\ X\ PERIOD) + ei$

where Yi is the value of the dependent variable for the i th patient, INTERVENTION is a dummy variable representing exposition to the program (INTERVENTION=1), PERIOD is a a dummy variable (0="before program implementation" period and 1="after program implementation" period). The coefficient of the interaction term (β 3) reflects the impact of the program).

[b] Defined as five or more units of ICS/LABA in a single inhaler and/or ICS as a single agent medicine, or 8 or more units of LTRA. This definition was issued from a scoping study provided by the CNAM (data not published).

[c] Defined as dispensation of oral or injectable corticosteroids within seven days of the GP visits.

[d] Defined as dispensation of R03 drugs within seven days of the GP visits.

[e] Defined as hospitalization, ER visits room or a visits to the general practitioner for exacerbation.

* Models were not run as the patients were different.

Table 3. Estimation of SA impact for patients in the intervention and unexposed groups, sub-group analysis.

	Patients with R03 ≥ 3 in the year prior to program implementation			Patients with R03 ≥ 1 in 2012			Patients with asthma as defined by the CNAM algorithm		
	OR or slope	95% CI	*P* value	OR or slope	95% CI	*P* value	OR or slope	95% CI	*P* value
Process outcomes									
Indicators of asthma control									
ICS+LTRA/R03≥0.5	0·98	(0·95 ;1·01)	0·2309	0·98	(0·95;1·02)	0·3347	0·92	(0·88;0·97)	**0·0014**
≥ 4 SABA	1·04	(1·00;1·08)	0·0630	1·02	(0·99 ;1·06)	0·1880	0·94	(0·90;0·99)	**0·0195**
Controller medication									
At least one controller medication dispensed	1·08	(1·04;1·13)	**0·0002**	1·06	(1·03;1·10)	**0·0006**	0·94	(0·88 ; 1·01)	0·1193
Sustained use of controller medication [a]	1·08	(1·04 ;1·13)	**<0·0001**	1·07	(1·03;1·11)	**0·0009**	1·04	(0·99 ; 1·09)	0·1114
Total no. of R03 dispensed, mean (SD)	0·51	(0·35 ;0·67)	**<0·0001**	0·39	(0·25 ; 0·52)	**<0·0001**	0·34	(0·09; 0·60)	**0·0080**
Adherence to controller asthma medications									
MRA>80%	1·09	(1·04;1·15)	**0·0007**	1·07	(1·02;1·13)	**0·0080**	1·08	(1·02;1·14)	**0·0139**
Healthcare utilization outcomes									
Urgent care visits									
At least one asthma-related hospitalization	0·51	(0·39;0·67)	**<0·0001**	0·50	(0·39;0·65)	**<0·0001**	0·55	(0·40;0·74)	**0·0001**
At least one ER visit for asthma	0·97	(0·90;1·04)	0·3588	0·97	(0·91;1·05)	0·4610	0·93	(0·84;1·02)	0·1024

At least one GP visit for asthma exacerbation [b]	0·98	(0·95;1·01)	0·2220	0·98	(0·95;1·01)	0·1652	0·94	(0·90;0·98)	**0·0071**
Routine visits									
At least one pulmonologist visit	1·01	(0·96;1·06)	0·6157	1·01	(0·96;1·06)	0·7163	0·99	(0·93;1·05)	0·7958
At least one routine asthma GP visit [c]	1·01	(0·98;1·05)	0·4411	1·02	(0·99;1·06)	0·1430	0·89	(0·84;0·94)	**<0·0001**
At least one pulmonary function testing	0·98	(0·94;1·03)	0·4548	0·98	(0·94;1·03)	0·4490	0·96	(0·90;1·02)	0·1700
Patient level outcomes									
At least one asthma exacerbation [d]	0·99	(0·96;1·02)	0·4722	0·99	(0·96;1·02)	0·3634	0·95	(0·91 ;0·99)	**0·0310**
Work absenteeism									
No. of sickleave days related to asthma, mean number (SD), days	-0·14	(-0·29; 0·02)	0·0934	-0·14	(-0·28;-0·01)	**0·0382**	-0·29	(-0·53 ;-0·05)	**0·0197**
At least one sickleave episode related to asthma	0·97	(0·90;1·04)	0·3403	0·96	(0·9; 1·03)	0·2625	0·92	(0·84 ;1·00)	0·0534

Data are no. (%) of patients, unless otherwise indicated. Values in bold indicate significant associations (p<0.05).

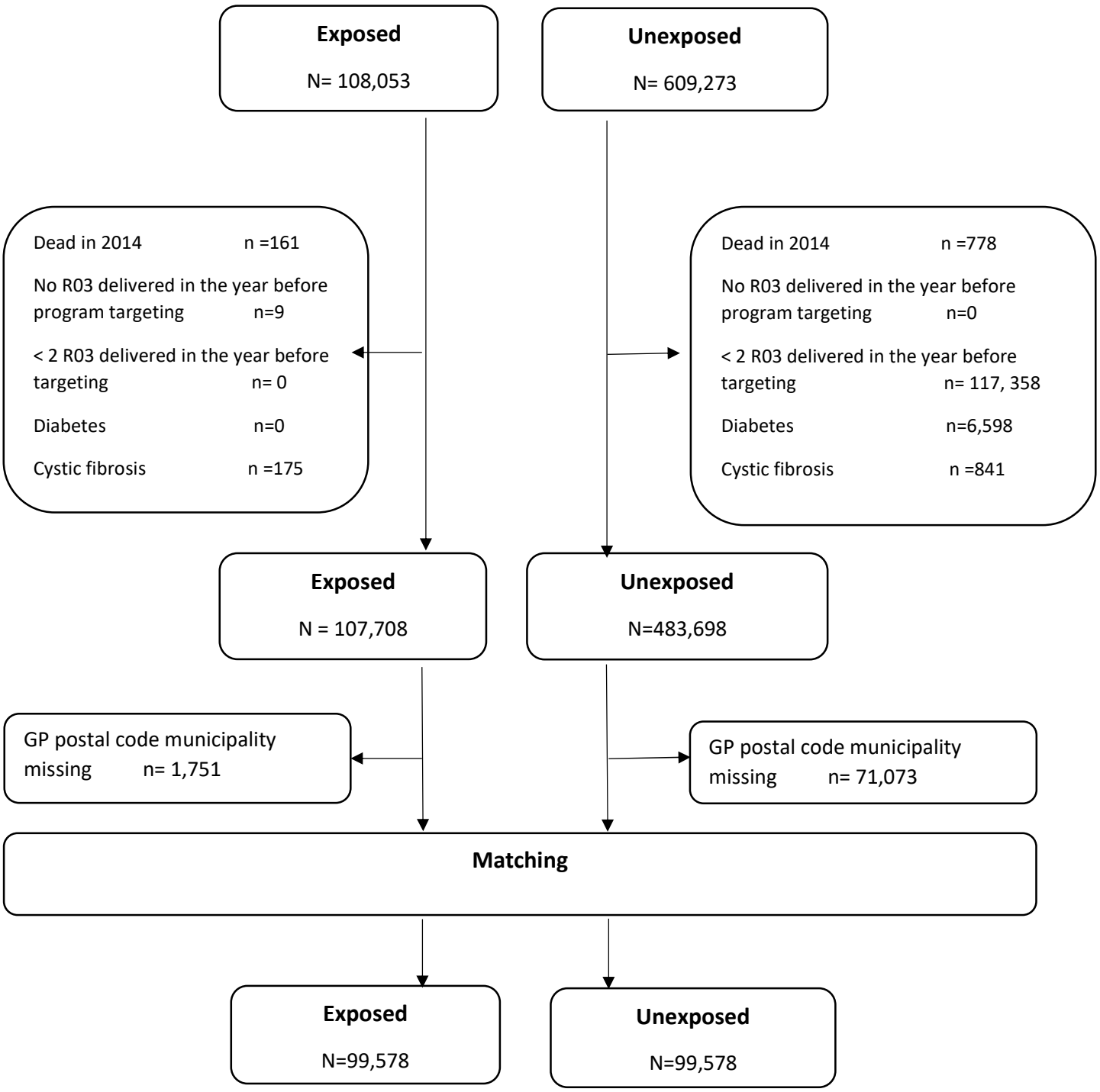
ER, emergency room; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β-agonists.

[a] Defined as five or more units of ICS/LABA in a single inhaler and/or ICS as a single agent medicine, or 8 or more units of LTRA. This definition was issued from a scoping study provided by the CNAM (data not published).

[b] Defined as hospitalization, ER visits room or a visits to the general practitioner for exacerbation

FUGURES

Figure 1 : Flow and selection of subjects records for inclusion into propensity analyses ;


Exposed
N= 108,053
Unexposed
N= 609,273
Dead in 2014 n =161
No R03 delivered in the year before program targeting n=9
< 2 R03 delivered in the year before targeting n= 0
Diabetes n=0
Cystic fibrosis n =175
Dead in 2014 n =778
No R03 delivered in the year before program targeting n=0
< 2 R03 delivered in the year before targeting n= 117, 358
Diabetes n=6,598
Cystic fibrosis n =841
Exposed
N = 107,708
Unexposed
N=483,698
GP postal code municipality missing n= 1,751
GP postal code municipality missing n= 71,073
Matching
Exposed
N=99,578
Unexposed
N=99,578