



Seasonal changes in prescribing of long-acting beta-2-agonists-containing drugs

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Summary

Background: For patients with asthma, COPD, or asthma-COPD overlap syndrome (ACOS), inter-country comparisons of seasonal changes in drug prescriptions are scarce or missing. Hence, we aimed to compare seasonal changes in prescription rates of long-acting beta-2-agonist (LABA) in four European countries.

Methods: A common study protocol was applied to six health care databases (Germany, Spain, the Netherlands (2), and the UK (2)) to calculate age- and sex-standardized point prevalence rates (PPRs) of LABA-containing prescriptions by the 1st of March, June, September, and December of each year during the study period 2002–2009. Seasonal variation of PPRs was quantified using seasonal indexes (SIs; based on the ratio-to-moving-average-method) and SIs averaged over the study period (aSI) stratified by sex, age, and indication (asthma, COPD, or ACOS).

Results: There was a moderate seasonal change in LABA-containing prescriptions which was more pronounced in asthma or COPD patients compared to ACOS patients. For asthma and ACOS patients, highest seasonal variation was found for patients living in Spain (aSI: 87.3–110.7, aSI: 93.2–103.1) whereas for COPD highest seasonal variation was revealed for the NPCRD database (the Netherlands) (aSI: 92.2–105.6). Regarding age and sex, highest seasonal variation was found in Spanish boys under 10 years of age having a diagnosis of asthma.

Conclusions: By applying a common analysis in six databases, we could observe moderate overall seasonal changes in LABA-containing prescription rates in patients with asthma, COPD, or ACOS.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are common, high-burden diseases resulting in disability and poor health-related quality of life [1]. In the last years it has been recognized that in particular in elderly patients, symptoms of asthma and COPD may overlap (i.e. asthma-COPD overlap syndrome [ACOS] [2,3]). Compared to asthma or COPD patients, worse clinical outcomes for ACOS patients were reported [4–7] but there are also somewhat conflicting data [8]. For asthma or COPD, there is good evidence for seasonal variations of clinically relevant endpoints (e.g. exacerbations leading to hospital admissions) [9–11] whereas comprehensive data are lacking for ACOS patients. For asthma patients, the highest numbers of exacerbations are reported in spring and/or in autumn, in particular in young children, e.g., in Finland, the United States, Greece, and Israel. Pollen exposure, viral infections, climate factors, and stress (e.g., at school after the summer holidays) were reported among others as major risk factors for asthma exacerbations [10,12–17]. In COPD patients, seasonal variations with highest exacerbation rates during the winter season were found [9,11]. Viral infections may contribute to this pattern, but the results presented in the literature are conflicting [18,19].

Limited data is available regarding periodical changes in prescription rates of respiratory drugs [20]. Nevertheless,

drug-related analyses might help to identify and quantify several treatment related problems such as undertreatment or the exacerbation-related increase in drug consumption. In addition, data comparing seasonal changes in drug prescriptions in different countries is lacking. However, additional data may help to understand seasonal changes and country-specific characteristics of drug prescribing to a greater extent. Thus, we aimed to analyse seasonal variations of prescriptions of long-acting beta-2-agonists (LABA), which is a widely used drug class and recommended for the treatment of COPD, asthma, and ACOS patients according to international guidelines [2,21].

To the best of our knowledge, we assessed and compared seasonal patterns and changes of LABA-containing prescriptions for the first time with a standardized method over an eight years period using six health care databases from four different European countries. This research was performed within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) [22].

Methods

Data sources

The study was performed using the following six European health care databases: Mondriaan–Netherlands Primary

Care Research Database (Mondriaan–NPCRD, The Netherlands) [23], Mondriaan–Almere Health Care Group (Mondriaan–AHC, The Netherlands) [24], The Clinical Practice Research Datalink (CPRD, United Kingdom) [25], The Health Improvement Network (THIN, United Kingdom) [26], Computerized Database for Pharmacoepidemiological Studies in Primary Care (BIFAP, Spain) [27], and The Bavarian Association of Statutory Health Insurance Physicians database (Bavaria, Germany) [28]. The different databases covered a regionally/nationally representative population between 170,000 and 10.5 million individuals. Details of all databases have been described elsewhere [29]. The International Statistical Classification of Diseases and Related Health Problems (ICD–10), the International Classification in Primary Care (ICPC), or Read Codes were used for coding diagnoses. The Anatomical Therapeutic Chemical classification system (ATC) or Multilex Codes were used for drug coding.

Study period and population

The defined study period was between January 1, 2002 and December 31, 2009. In two databases, the study period differed slightly (Bavaria: 2004–2008; Mondriaan–AHC: 2002–09/2009). The study population comprised all patients of each database that were stored with valid data, active registration status, and a diagnosis of COPD and/or asthma. The indication was defined retrospectively starting at the date of the last LABA-containing prescription within the study period and screening the entire study period backwards searching for appropriate medical codes used to classify patients into three mutually exclusive categories of “asthma”, “COPD”, or “asthma and COPD”. Patients having a diagnosis of asthma and COPD (“asthma and COPD”) were considered as ACOS patients (codes see e-table 1–table 4).

Exposure definition

Exposure was defined as at least one prescribed inhaled LABA (salmeterol (ATC code R03AC12) or formoterol (R03AC13)) including fixed combination drugs (codes see e-table 5, e-table 6) irrespective of any other concomitant medication.

Statistical analysis

All analyses were stratified by indication (“asthma”, “COPD”, or “asthma and COPD” (ACOS)). Taking into account seasonal variations, point prevalence rates were calculated by the 1st of March, 1st of June, 1st of September, and 1st of December of each year during the study period as follows: the number of patients being prescribed a LABA-containing drug that covered the specific dates, divided by the number of patients available in the database at those specific dates. We considered all LABA-containing drugs prescribed on the selected dates (1st of March, 1st of June, 1st of September, 1st of December) or before, taking into account an episode of drug coverage including those dates. The expected duration of each LABA-containing prescription was estimated using the prescribed

quantity based on package sizes and the prescribed daily dose or in case of missing data, the age-group median duration of use of the specific database was used (CPRD and BIFAP database). As these parameters were often unknown in the remaining databases, a time period of 90 days was used as surrogate for the duration of a prescription. In order to adjust for potential inter-database differences in the source populations’ age and sex distribution, standardized point prevalence rates were calculated by using direct standardization based on the 2008 European reference population [30].

Seasonal variation was measured in terms of seasonal indexes (SIs). For the calculation of SIs, standardized point prevalence rates were analysed using the ratio-to-moving-average-method [31]. For each quarter within the study period (1st March, 1st June, 1st September, 1st December), a separate SI was calculated. Each SI represented a percentage value, with an annual average equal to 100; hence, each quarterly SI indicated the particular point prevalence rate of LABA-containing prescriptions in relation to the annual average of 100. An SI <100 or >100 indicated that the point prevalence rate for the quarter of interest was below or above the average for the year. If the four SIs of one year did not sum up to 400 due to rounding differences, a correction factor was applied to each SI to force the sum to 400 resulting in adjusted SIs.

For estimating seasonality for the whole study period (and for smoothing yearly specifics), averaged SIs (aSIs) were calculated for each of the three patient groups. For the calculation of an aSI for the 1st, 2nd, 3rd, and 4th quarter, the adjusted SIs were averaged overall years within the study period for the respective database. Finally, the seasonal index difference (delta-aSI) was calculated as the difference of the maximum and the minimum aSI value in order to quantify the magnitude of seasonality.

All SI calculations were stratified by sex and age groups “0–9”, “10–19”, [...], “70–79”, and “≥80 years” for “asthma” and “40–49”, “50–59”, [...], “70–79”, and “over 80 years” for “COPD” and “asthma and COPD”.

Results

Asthma

The point prevalence rates of LABA-containing prescriptions increased in asthma patients in all databases from 2002 onwards (Fig. 1). In March 2002, age- and sex-standardized point prevalence rates of LABA-containing prescriptions varied between 415 per 10,000 persons (CPRD) and 701 per 10,000 persons (Mondriaan–AHC) and increased continuously over time. At the end of the study period, age- and sex-standardized point prevalence rates ranged between 1026 per 10,000 (BIFAP) persons and 1684 per 10,000 persons (Mondriaan–NPCRD).

Seasonality of LABA-containing prescriptions

In all databases, the lowest aSI indicating the quarter with the lowest number of LABA-containing prescriptions was found on 1st September (range: 87.3% [BIFAP] – 98.5% [CPRD, Mondriaan–AHC], Table 1). The highest aSI value

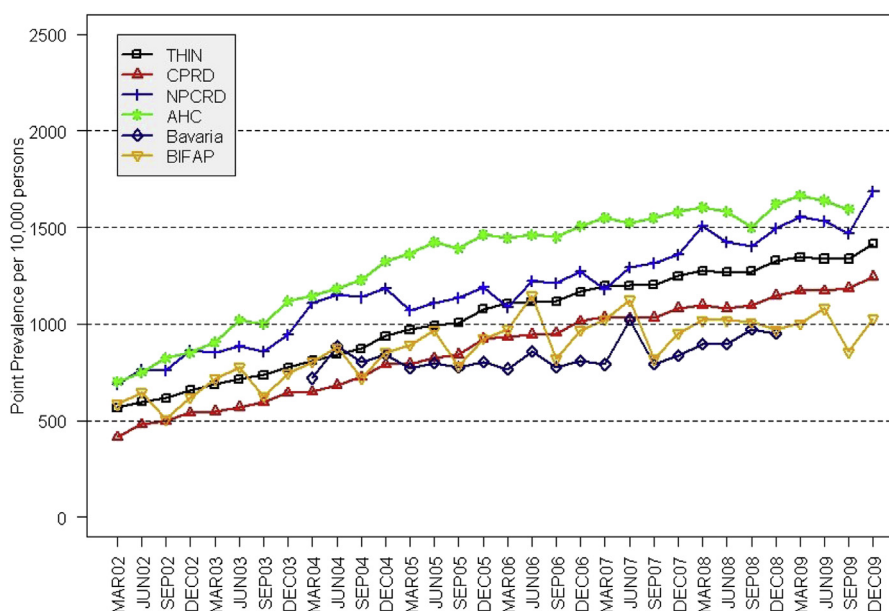


Figure 1 Point prevalence rates for LABA-containing prescriptions in asthma patients per 10,000 persons.

(i.e. the highest number of LABA-containing prescriptions) was observed on 1st December for the CPRD and Mondriaan–NPCRD databases (102.1% and 101.6%), 1st March for the THIN database (101.0%), and 1st June for the remaining databases (BIFAP: 110.7%; Bavaria: 106.7%; and Mondriaan–AHC: 100.6%, [Table 1](#)).

Averaged seasonal indexes for THIN, CPRD, Mondriaan–NPCRD, and Mondriaan–AHC were very stable over the years with an overall delta-aSI between 2.2 and 3.7, indicating no relevant seasonal variations of LABA-containing prescriptions ([Table 1](#)). Seasonal differences in prescribing behaviour were more evident in the Bavarian database (delta-aSI = 10.4; [Table 1](#)). In the BIFAP database, the highest seasonal impact on LABA-containing prescriptions was detected (delta-aSI = 23.4; [Table 1](#)). The SIs for each separate quarter are presented in [Fig. 2](#).

Seasonal index stratified by sex and age

When comparing the delta-aSI values between men and women, there was no visible difference in the CPRD and THIN databases ([e-Fig. 1](#)). Whereas in the BIFAP and Bavarian database small differences were found between the sexes in some age groups, the sex-related difference was most pronounced in the Dutch databases (Mondriaan–NPCRD: age groups 0–9 years and 70–79 years on 1st

March; Mondriaan–AHC: age groups 70–79 years on 1st March and ≥80 years on 1st June).

Delta-aSIs differed tremendously with age in all databases. The seasonal variation was very distinct in the youngest age group (0–9 years) in the CPRD, THIN, Mondriaan–NPCRD, and BIFAP databases. The delta-aSI varied from 12.2 (THIN) to 79.3 (BIFAP) in boys and from 12.6 (Bavaria) to 74.4 (BIFAP) in girls ([e-Fig. 1](#)). For the Bavarian database and for men in the Mondriaan–AHC database, the highest delta-aSI was found in individuals aged 20–29 years. The impact of seasonality on LABA-containing prescriptions was less prominent with increasing age and the delta-aSIs for each date became quite similar.

COPD

The age- and sex-standardized point prevalence rates of LABA-containing prescriptions for patients with a documented COPD diagnosis varied between 124.1 per 10,000 persons and 1063.3 per 10,000 persons in the year 2002. LABA-containing prescriptions increased over time and the point prevalence rates at the end of the study period ranged between 945.5 per 10,000 persons and 2341.6 per 10,000 persons. For the whole study period, point prevalence rates of LABA-containing prescriptions were the highest in the Dutch databases ([Fig. 3](#)).

Seasonality of LABA-containing prescriptions

For all databases, lowest aSIs were found on 1st September (range: 91.8% [BIFAP] – 98.9% [CPRD]) and highest on 1st December (Mondriaan–NPCRD: 105.6%; Bavaria: 104.5%; and CPRD: 101.8%), 1st March (BIFAP: 104.8%) or 1st June (Mondriaan–AHC: 101.8%, THIN: 101.8%; [Table 2](#)). The weakest seasonality effect was found in the CPRD and THIN databases (delta-aSI: 2.8 and 4.5), whereas delta-aSIs varied between 6.1 and 13.4 for the remaining databases ([Table 2](#)). SIs for each quarter and database are visualized in [Fig. 4](#).

Table 1 Averaged seasonal indexes (aSIs) and seasonal index difference (delta-aSI) for asthma patients; NPCRD: Mondriaan–NPCRD; AHC: Mondriaan–AHC.

	THIN	CPRD	NPCRD	AHC	Bavaria	BIFAP
aSI March	101.0	100.3	99.7	100.2	97.0	103.5
aSI June	99.7	99.1	100.8	100.6	106.7	110.7
aSI September	98.4	98.5	97.9	98.5	96.3	87.3
aSI December	100.8	102.1	101.6	100.6	100.0	98.4
Delta_aSI	2.6	3.7	3.7	2.2	10.4	23.4

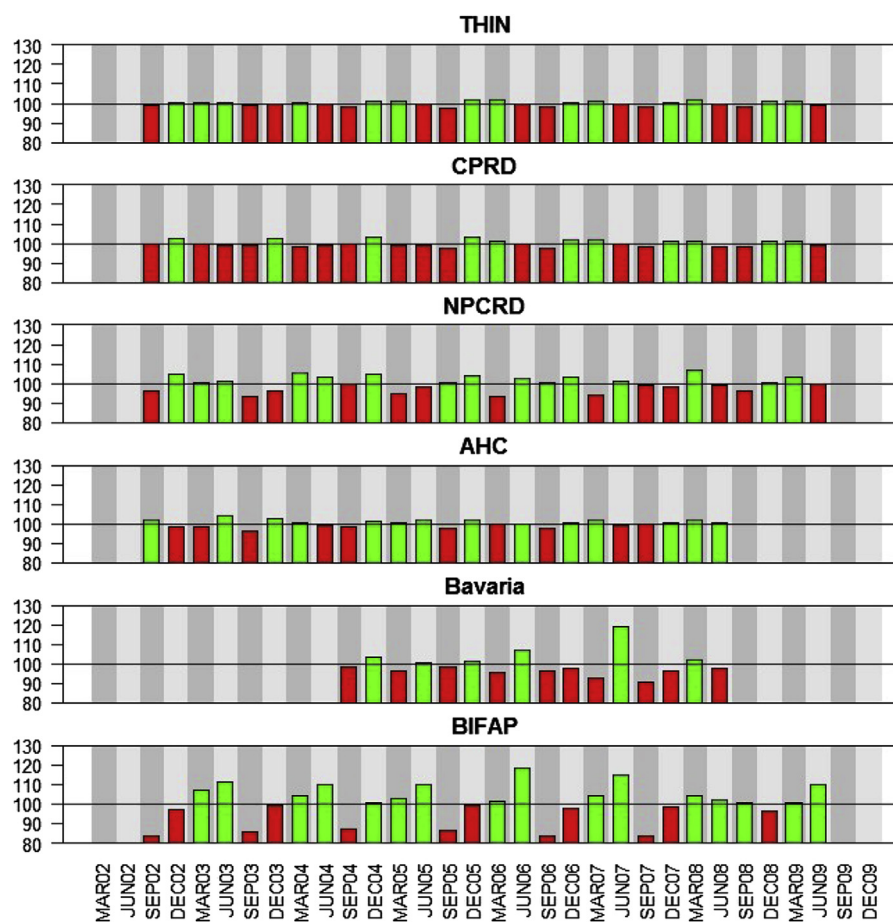


Figure 2 Seasonal index for LABA-containing prescriptions in asthma patients.

Seasonal index stratified by sex and age

Regarding mean values for all databases, slightly higher delta-aSIs were found for females compared to men (except for patients aged between 70 and 79 years). In THIN, delta-aSIs were higher in men compared to women for all age groups (10.6–13.1%), whereas in Mondriaan-AHC, women aged ≥ 80 years had higher delta-aSI values than men in this age group (e-Fig. 2). For most databases highest delta-aSIs were found in age groups 40–49 and ≥ 80 (e-Fig. 2).

Asthma-COPD overlap syndrome (ACOS, “asthma and COPD”)

An increase of the age- and sex-standardized point prevalence rates of LABA-containing prescriptions for ACOS patients was found for all databases within the study period. For the whole study period, point prevalence rates of LABA-containing prescriptions were the highest in the THIN database (2002: 1484.9 per 10,000 persons; 2009: 4004.1 per 10,000 persons) and the lowest in the BIFAP database (2002: 1112.5 per 10,000 persons; 2009: 2050.0 per 10,000 persons) (Fig. 5).

Seasonality of LABA-containing prescriptions

For most databases, lowest aSIs were found on 1st September (range: 93.2% [BIFAP] – 99.1% [THIN]) and highest on 1st December (THIN: 100.6%; CPRD: 102.2%;

Mondriaan-NPCRD: 104.7; Bavaria: 103.6), or 1st March (BIFAP: 103.1%; Mondriaan-AHC: 101.3%, Table 3). For the two UK databases and the Mondriaan-AHC database the delta-aSI were within the range of 1.4–3.5. For the remaining databases seasonal differences in LABA-prescribing behaviour were more evident (delta-aSI varied between 6.1 and 9.9; Table 3). SIs for each quarter and database are shown in Fig. 6.

Seasonal index stratified by sex and age

The averaged delta-aSIs for all databases were higher for females for all age classes except for patients between 70 and 79 years. The highest aSIs were found in the age groups 40–49 and ≥ 80 (e-Fig. 3).

Discussion

By using a common methodology and analysing prescribing data of six European databases from four countries, we found an increase in PPRs for LABA-containing prescribing during the study period for patients diagnosed with asthma, COPD, or ACOS. Regarding the main focus of our study, i.e. seasonal variations of LABA-containing prescriptions, we found only moderate seasonal changes in prescriptions of LABA-containing drugs for the three patient groups. This is in line with the respective guidelines recommending these medicine as maintenance treatment [2,21]. For all three

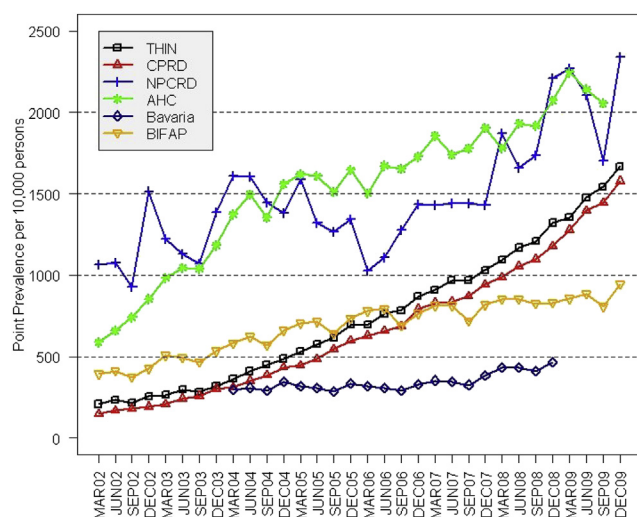


Figure 3 Point prevalence rates for LABA-containing prescriptions in COPD patients per 10,000 persons.

indications, we found lowest aSIs in most databases for the 1st September covering prescriptions of the summer period. Regarding risk factors for developing asthma and COPD [9–19], seasonal variations showing lowest exposure for some risk factors during the summer period might be causal. In addition, the vacation period itself might be of relevance in terms of shifting prescriptions before or after the summer holidays. Taking into account these issues, undertreatment has been proposed as a possible explanation for asthma exacerbations after summer holidays [16].

Asthma

In one of the few studies focussing on seasonal changes in drug dispensing, temporal changes were found for respiratory drugs by analysing nation-wide claims data of children living in the United States [20]. In this study, periodical changes were more pronounced compared to our analysis, but several methodological differences have to be considered (e.g. inclusion of typically seasonally used antihistaminic agents, non-consideration of indication, shorter period for prevalence calculation), limiting the comparability of results. Nevertheless, similar to our overall study results, lower dispensing rates were found for respiratory drugs during the summer period [20].

Regarding the age-related aspects of seasonality, younger patients have been reported to be more likely to

experience seasonal changes in asthma exacerbations and emergency department visits [16,17]. This is in line with our results, showing most pronounced seasonal changes in LABA-containing prescriptions in the youngest age group (0–9 years) in all databases (except the Bavarian database (male and female patients) and the Mondriaan-AHC database (male patients), where we observed the highest variations in patients aged 20–29 years). For younger ages somewhat higher seasonal changes in asthma exacerbation rates were reported [12,17], while in our study age-related differences in LABA-containing prescriptions might have been masked to some extent by the use of 10-year age categories.

By assessing inter-country differences in prescribing patterns, we found a wide variation of seasonal index differences with lowest and highest values in the CPRD and the Spanish database. Despite limited generalizability of seasonal data from other geographical regions, somewhat similar geographical latitude-related differences were found in a Finnish study. Compared to Northern Finland higher asthma exacerbation rates were found in Southern Finland which were mainly attributed to an increased pollen burden [12]. Other climate factors, increasing or decreasing the risk for asthma exacerbations (e.g. ozone, temperature, sunshine duration [17]), might have also contributed to the inter-country variations observed in our study. For differences in maximum LABA-prescription prevalence rates, regional variations of climate factors as well as other risk factors for asthma exacerbations (e.g. viral infections) might be causative [32–36].

COPD

For COPD patients, only limited data regarding seasonal changes in drug prescriptions is available. In a post-hoc analysis of a large, randomized trial, seasonal differences in rates of exacerbations and treatment were found with highest rates in the winter season. An increased utilization of antibiotics and oral corticosteroids was suggestive of more severe exacerbations during the winter [9,11]. This is in line with our study, showing highest prevalence of LABA-containing prescriptions during the autumn and winter period (1st December and 1st March point prevalence) in most databases. As observed in patients diagnosed with asthma, the lowest rate of LABA-containing prescriptions was found for the third quarter (point prevalence 1st September), which is also in line with results from other studies [9,11].

For COPD patients, we found no clear age-related seasonal changes in LABA-containing prescriptions, which is in concordance with results from other studies, stating no influence of age on COPD exacerbation rates [11]. Interestingly, seasonal changes in prescriptions of LABA-containing drugs were more prominent in our analysis in women than in men diagnosed with COPD. There are only a few sex-related analyses on this topic mentioned in the literature, indicating no significant influence of sex on clinical endpoints [11,37].

Regarding inter-country differences, we found a less pronounced variation of LABA-containing prescriptions between the countries for COPD patients compared to our

Table 2 Averaged seasonal indexes (aSIs) and seasonal index difference (delta-aSI) for COPD patients; NPCRD: Mondriaan-NPCRD; AHC: Mondriaan-AHC.

	THIN	CPRD	NPCRD	AHC	Bavaria	BIFAP
aSI March	99.7	99.4	104.9	101.2	103.8	104.8
aSI June	101.8	99.9	97.3	101.8	99.7	103.5
aSI September	97.3	98.9	92.2	95.7	91.9	91.8
aSI December	101.1	101.8	105.6	101.2	104.5	99.9
Delta-aSI	4.5	2.8	13.4	6.1	12.5	13.0

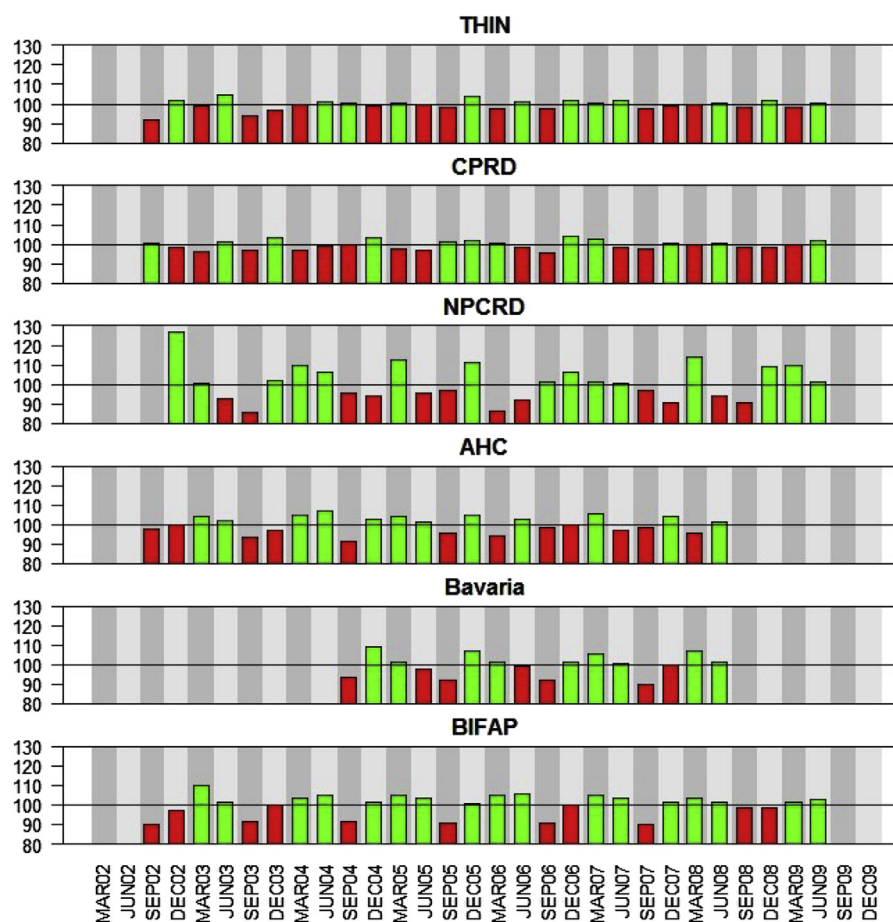


Figure 4 Seasonal index for LABA-containing prescriptions in COPD patients.

analyses in asthma patients. Nevertheless, similar to the results for asthma patients, inter-country differences in viral infections might have contributed to the differences in maximum prevalence rates.

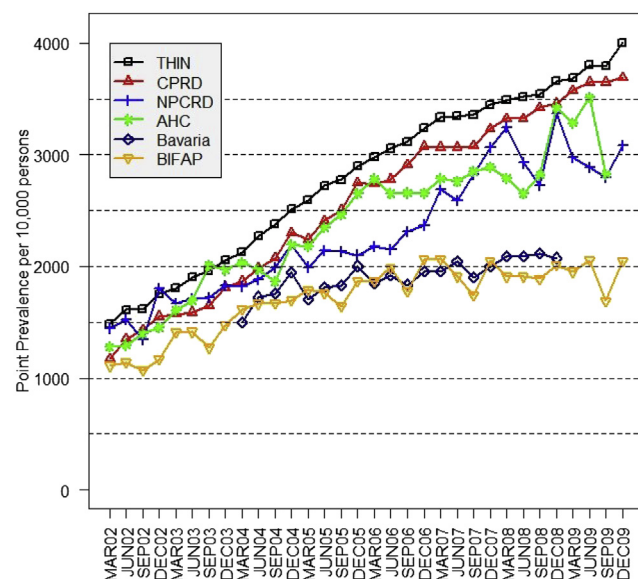


Figure 5 Point prevalence rates for LABA-containing prescriptions in patients with asthma-COPD overlap syndrome (ACOS patients) per 10,000 persons.

ACOS (asthma-COPD overlap syndrome)

In our study, we found highest PPR rates for LABA-containing prescriptions for ACOS patients in all databases within the study period. This is supported by clinical data showing an increased risk for exacerbations and hospitalizations in ACOS patients compared to patients suffering from asthma or COPD [4–6]. Regarding seasonality, we found lowest averaged seasonal indexes (aSI) on the 1st September which is in line with our data for asthma patients or COPD patients showing the same pattern. Whereas in three databases (CPRD, Mondriaan-NPCRD, Mondriaan-AHC) delta-aSIs of ACOS patients laid between of those calculated for asthma or COPD patients, delta aSI were lowest in ACOS patients in the three remaining databases.

Table 3 Averaged seasonal indexes (aSIs) and seasonal index difference (delta-aSI) for patients with asthma-COPD overlap syndrome (ACOS patients); NPCRD: Mondriaan-NPCRD; AHC: Mondriaan-AHC.

	THIN	CPRD	NPCRD	AHC	Bavaria	BIFAP
aSI March	100.0	99.8	101.0	101.3	98.2	103.1
aSI June	100.3	99.1	98.0	97.8	100.8	102.1
aSI September	99.1	98.9	96.3	99.8	97.4	93.2
aSI December	100.6	102.2	104.7	101.1	103.6	101.6
Delta-aSI	1.4	3.3	8.4	3.5	6.1	9.9

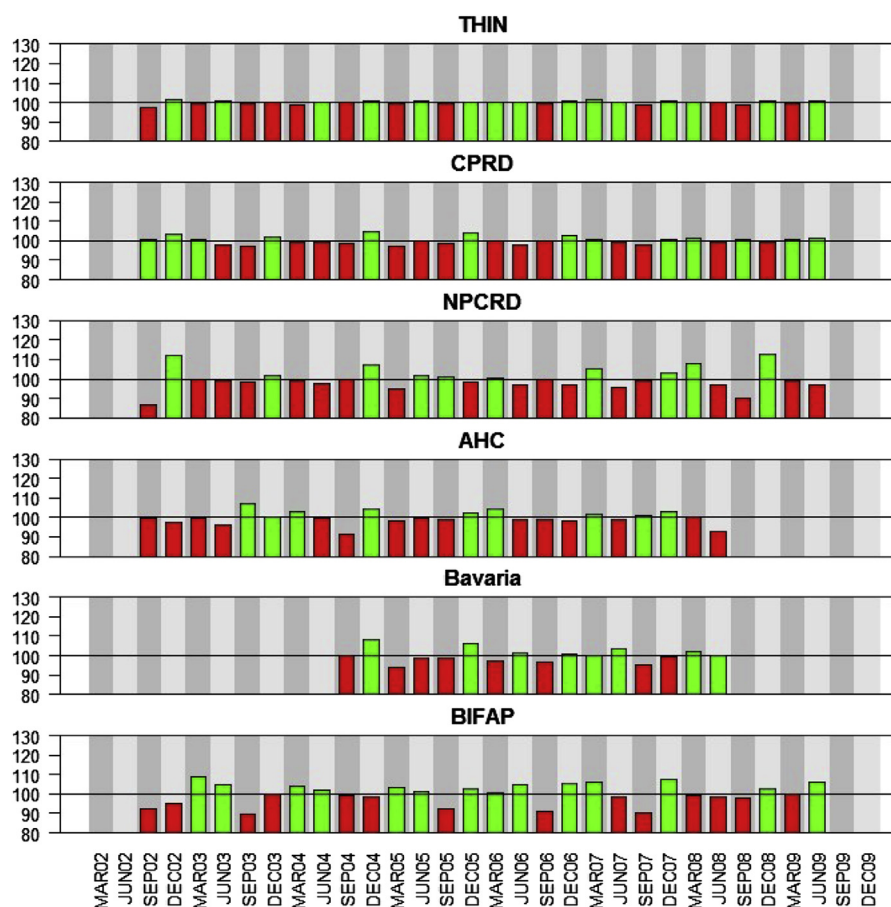


Figure 6 Seasonal index for LABA-containing prescriptions in patients with asthma-COPD overlap syndrome (ACOS patients).

Taken together, less prominent seasonal changes in LABA-prescribing were found in some databases underlining the need of continuous LABA-prescribing in ACOS patients due to the severity of clinical symptoms [4–6].

Strengths and limitations

This study has a number of strengths and some limitations. As a major strength, we consider the inclusion of different databases from several countries, the coverage of different populations, and the use of a common protocol in our study. There are also some limitations to our study. Firstly, by using four data points for the calculation of the point prevalence rates per year to represent the number of LABA-containing prescriptions we might have underestimated the magnitude of seasonal changes in LABA-prescriptions compared to other studies using e.g. 12 data points per year [20]. Secondly, there are some difficulties in diagnosing asthma, COPD, or ACOS under real-life conditions [7,38,39]. As in most multi-national database studies, we abstained from validating diagnoses by using e.g. lung function parameter for feasibility reasons and lacking data in some databases. Hence, we cannot exclude as misclassification of patients considered as asthma, COPD, or ACOS patients in our study. Third, the interpretation of seasonal changes in LABA-containing prescriptions as a proxy for clinical endpoints (e.g. exacerbations) is limited for several reasons: In patients with more severe asthma or COPD, receiving LABA for a prolonged period of time, no seasonal

changes in treatment may be noticed assuming that the patients are persistent with therapy. On the other hand, patients with mild asthma, receiving short-acting beta-2-agonists will not be included in our study if they have received inhaled corticosteroids only (without LABA) during their asthma exacerbation. The same issue is present in COPD patients if they have received tiotropium (a long-acting muscarinic agonistic (LAMA)) instead of LABA for treating exacerbations. Furthermore, we did not discriminate between drugs consisting of LABA only and drugs containing both, LABA and inhaled corticosteroids. Despite these limitations, we found a similar periodical pattern of LABA-containing prescriptions compared to clinically relevant endpoints in asthma and COPD as stated above. In future studies - by analysing the association between risk factors for exacerbations (e.g. climate factors), drug usage and clinically endpoints on an individual patient base - high-risk situations and high-risk patients could be identified and prevention strategies for reducing exacerbations could be developed.

Conclusion

By applying a common study protocol to data from six European databases, we could show moderate overall seasonal changes in LABA-containing prescriptions which was more pronounced in asthma or COPD compared to ACOS

patients. After stratification by age and sex, we found considerable seasonal changes in LABA-containing drug prescriptions. The most pronounced variation of LABA-containing prescription rates was found for asthma and ACOS in patients living in Spain and for COPD patients documented in the national Dutch database (Mondriaan-NPCRD). Regarding age and sex, highest seasonal variation was found in boys aged younger 10 years living in Spain and having a diagnosis of asthma. Further studies are needed to analyse whether these inter-country differences in seasonal prescription rates lead to differences in clinical relevant endpoints.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2015.01.010>.

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