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ORIGINAL RESEARCH

Dispensing Patterns of Inhaled Asthma Medication Before and During COVID-19 Among Young Adults in the Netherlands: A Retrospective Inception Cohort Study

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Background: The impact of the coronavirus disease 2019 (COVID-19) pandemic on asthma medication trajectories, including changes in medication type or dosage, remains unclear. This study compared dispensing patterns among adults who initiated asthma inhalers before pandemic (cohorts 2014 and 2017) and during pandemic (cohort 2020).

Methods: We performed retrospective inception cohort study using University of Groningen IADB.nl community pharmacy dispensing database. Individuals aged 16–44 years who initiated inhaled asthma treatment in 2014, 2017, or 2020 were followed for 2 years. Treatment steps (1–5) were based on the Global Initiative for Asthma (GINA) guideline. Primary outcomes included time to treatment step switch (step-up or step-down) and time to first oral prednisolone/prednisone, and were compared between cohorts using Cox regression models.

Results: In 2014, 2017 and 2020, 1193, 960 and 730 patients initiated asthma inhalers, respectively. In all cohorts, more than half of the patients initiated treatment at the lowest step. During 2-year follow-up, fewer patients switched their treatment steps in 2020 when compared with 2014 (adjusted hazard ratio (aHR): 0.86 (95% confidence interval (CI): 0.76–0.99). From 2014 to 2020, the likelihood of treatment stepping-down decreased over time, with a 21% in 2017 (aHR: 0.79 (0.68–0.92)) and 24% in 2020 (aHR: 0.76 (0.64–0.90)) compared to 2014, while the likelihood of stepping-up did not change significantly. The risk of taking oral prednisolone/prednisone was also significantly lower in 2020 (aHR: 0.76 (0.61–0.94)).

Conclusion: During the pandemic, fewer asthma patients switched treatment steps and took oral prednisolone/prednisone. Since 2014, fewer individuals stepping down medication, with a decrease of 21% in 2017 and 24% in 2020. Possible drivers include improved adherence, better asthma control, and increased telemedicine use—trends that predate and have been accelerated by the pandemic. Research incorporating clinical data is necessary to confirm these hypotheses.

Keywords: asthma, COVID-19, inhaled medication, treatment step, trajectory, GINA

Introduction

Asthma affects an estimated 262 million people worldwide,[1] of which 1.2 million in the Netherlands.[2] The primary goal of asthma management is to achieve optimal symptom control and reduce the risk of exacerbations while minimizing the adverse effects of treatment.[3] Controller inhalers are used on a daily basis to prevent airflow obstruction and

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exacerbations, while reliever inhalers are used to relieve acute asthma symptoms. The Global Initiative for Asthma (GINA) recommends a stepwise strategy that allows the intensity of treatment to be adjusted (stepping-up or -down) according to the severity of the disease, the symptoms present, and future risk of exacerbation. Notably, the goal is to control at the lowest possible dose and avoid unnecessarily high doses with increased risk of adverse events.[4] Previous studies by Gayle et al and our group have shown a generally low frequency of treatment transitions between different steps of asthma management.[5,6] The low number of patients moving between steps may indicate that the prescribed treatment is well matched to the severity of their asthma and reflects well-controlled asthma without any side effects, or it may be the result of clinician inertia, either fearing the risk of adverse events by stepping up or fearing uncontrolled asthma by stepping down.[7]

The coronavirus disease 2019 (COVID-19) pandemic has had a dramatic impact on healthcare services, and people with asthma were particularly vulnerable to these changes due to their need for long-term medical monitoring.[8] It has been reported that the number of clinical consultations decreased after the onset of the COVID-19 pandemic in the Netherlands.[9] This decrease in routine clinical visits could potentially lead to delayed asthma diagnosis and assessment of disease status, which in turn could delay initiation of appropriate treatment modifications, medication appraisal, and medication refills. A cross-sectional study found that only half of asthma patients were well-controlled in 2020, the first year of the COVID-19 pandemic.[10]

Conversely, multiple studies documented that asthma patients had improved asthma control during the pandemic, including improved adherence to asthma medications,[11,12] significantly reduced asthma exacerbations frequency,[13,14] and reduced use of oral prednisolone.[15] Improved asthma control was likely influenced by stay-at-home COVID-19 policies that reduced exposure to asthma triggers.[16] Moreover, severe and poorly-controlled asthma have been shown to increase the risk of severe COVID-19.[17,18] These concerns and fears about COVID-19 may also enhance patient awareness of the importance of asthma control.

Although the potential influence of the COVID-19 pandemic on asthma management (eg medication adherence, exacerbation frequency) has been investigated in previous studies, there is a lack of evidence regarding how overall dispensing patterns of asthma controller medications, such as changes in medication types or adjustments in dosing regimen, were affected during the COVID-19 pandemic. The aim of this descriptive study is to identify the dispensing patterns of new asthma inhaler users, comparing those who initiated asthma inhalers before the COVID-19 pandemic (in 2014 and 2017) with those who initiated during the COVID-19 pandemic (in 2020). We intend to identify changes in medication dispensing trends, with a focus on assessing the impact of the COVID-19 pandemic on real-world asthma management. We propose two hypotheses: 1. a smaller proportion of individuals adjust their treatment intensity (either step-up or step-down) due to a reduction in clinical visits and fear of COVID-19 during the pandemic; 2. a smaller proportion of individuals use oral corticosteroids, such as prednisolone or prednisone, due to decreased exposure to asthma triggers resulting from pandemic-related restrictions. This research may enable us to provide insights into the resilience of asthma medication patterns during the global pandemic and inform future healthcare strategies.

Methods

Study Design

We conducted a retrospective observational, longitudinal, inception cohort study of Dutch adults initiating inhaled asthma medication.

Data Source and Setting

The study period was from January 2014 to December 2022. Data were obtained from the IADB.nl (previously known as InterAction Database) pharmacy dispensing database of the University of Groningen, The Netherlands. This database contains all dispensing records from approximately 120 community pharmacies from all over the Netherlands, the majority of which are located in the northern region (Groningen, Friesland, Drenthe, etc) of the Netherlands, and covers more than 1.2 million individuals for more than 27 years. The IADB.nl database

undergoes rigorous cleaning and validation to ensure accuracy. Prescription records from community pharmacies are standardized using anatomical therapeutic chemical (ATC) codes and general practitioner (GP) registry linkage. Automated checks remove duplicates, and plausibility filters exclude implausible entries. Anonymized patient data remain linkable for longitudinal tracking. Internal validation cross-checks pharmacy logs, while external validation compares the population composition and the prevalence of drug use with national health registries Geneesmiddelen Informatie Project (GIP) databank (https://www.gipdatabank.nl/). The IADB.nl database has been shown to be representative of the entire Dutch population in terms of age distribution and the prevalence of drug use.[19] Regular audits ensure high data completeness and coverage. The database is updated every year. All prescription drugs are registered at the participating pharmacies for financial declarations. The dispensing data include an anonymous patient identifier, sex, date of birth, complete information on the dispensed drug, the dispensing date, the prescribed daily dose, and the number of drug units dispensed. IADB.nl lacks data on over-the-counter (OTC) drugs and hospital dispensing. However, this has a minimal impact on our results. In the Netherlands, inhaled asthma medications are only available on prescription and cannot be purchased over the counter. Hospital stays for asthma are typically short, with short-term medication use. Patients quickly transition to primary care and community pharmacies for ongoing prescriptions, which are captured in IADB.nl. These factors ensure that the database adequately represents asthma medication dispensing patterns.

Study Population

Similar to a previous study examining asthma medication dispensing trajectories in general,[5] we have the following inclusion criteria: (1) we included individuals who initiated inhaled asthma treatment with: short-acting beta-agonist (SABA), long-acting beta-agonist (LABA), inhaled corticosteroids (ICS), or a fixed-dose combination of ICS and LABA (ICS-LABA); (2) individuals were required to have at least one subsequent dispensing within 12 months of the first dispensing; (3) patients had to be in the database for at least 12 months prior to their first dispensing of asthma inhaled medication and had to have no corresponding dispensing one year prior to their first dispensing to ensure asthma treatment-naïve status (no corresponding dispensing in the prior year); (4) individuals had to be present in the IADB.nl database and have at least two years of follow-up data after the first dispensing of asthma inhaled medication. Details of the medications required for inclusion and other medications included in the analyses are listed in Table S1. To exclude pediatric patients with asthma, patients being < 16 years of age at initiation were excluded. To exclude possible patients with chronic obstructive pulmonary disease (COPD), individuals were excluded if they were ≥ 45 years old at initiation, or if they initiated treatment with LABA or tiotropium only (without ICS), or if they received roflumilast. The age of 45 as a cut-off point because people diagnosed with COPD outnumber people diagnosed with asthma after the age of 45.[20]

Figure 1a illustrates the structures of the cohorts of this study. Patients were categorized into three cohorts based on the year of initiation: cohort 2014 (pre-pandemic cohort, individuals who initiated in 2014, and were followed up until December 31, 2016); cohort 2017 (pre-pandemic cohort, individuals who initiated in 2017, and were followed up until December 31, 2019); cohort 2020 (pandemic cohort, individuals who initiated after March 1 2020, and were followed up until December 31, 2022). The years 2014, 2017, and 2020 were selected to allow for two years of follow-up and one year of washout and to avoid temporal overlap between cohorts. The two pre-pandemic cohorts can serve as a self-comparison to examine temporal trends predating COVID-19. For example, the 2015 Dutch College of General Practitioners (NHG) guideline, which emphasizes spirometry for distinguishing asthma from COPD and monitoring patients with uncontrolled asthma,[21] may have already influenced clinical practices prior to the pandemic. The start of the COVID-19 pandemic and the subsequent restrictions in the Netherlands occurred on March 1 2020.[15] To be consistent with the pandemic cohort, both cohort 2014 and cohort 2017 included only those who initiated their medications after March 1.

Treatment Steps

We assigned individuals into different treatment steps based on the December 2022 guidelines for adult asthma from the NHG, which align closely with the GINA recommendations.[4,22] These steps were as follows and illustrated in Figure 1b:

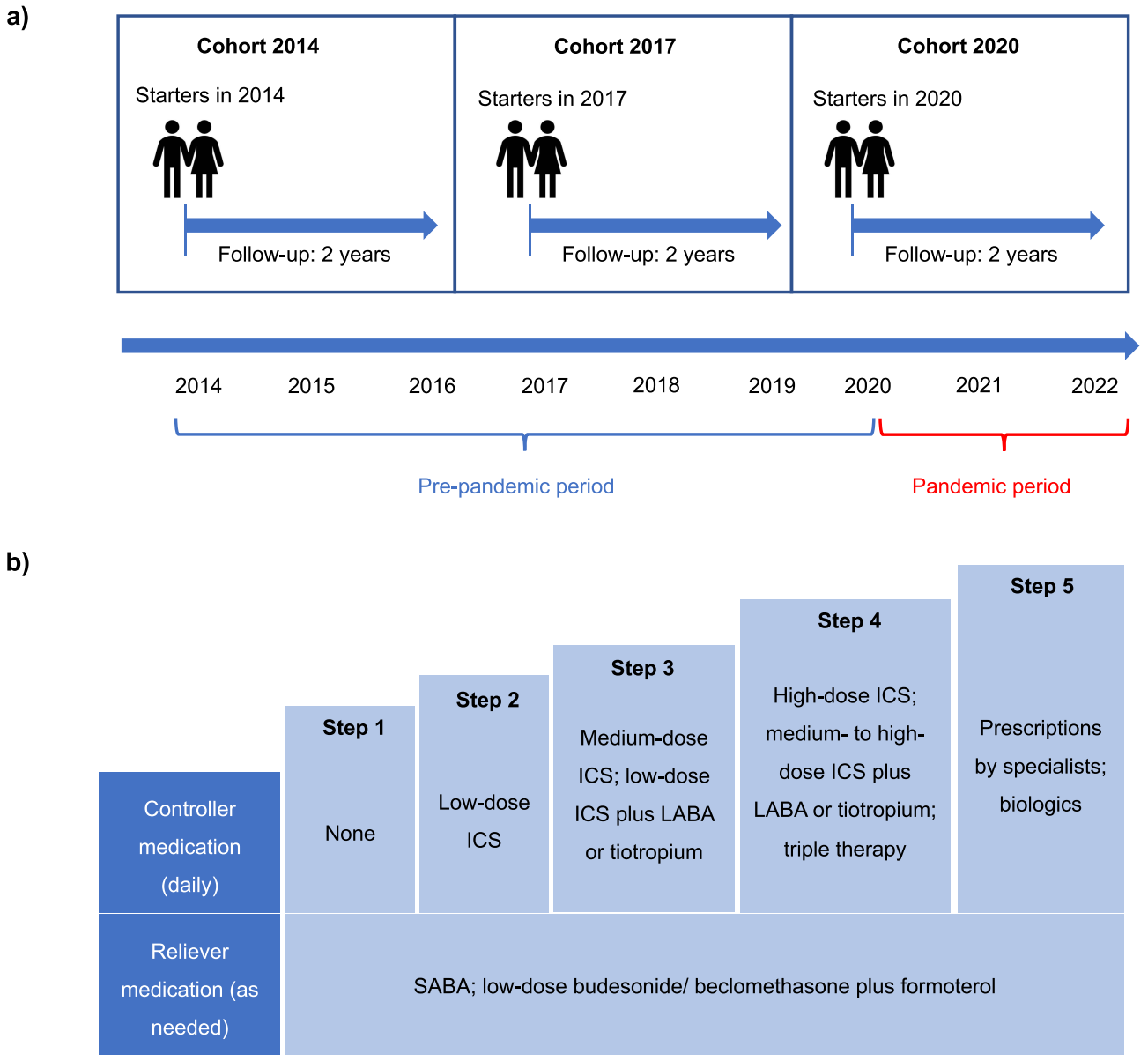

Figure 1 (**a**) The structures of cohort 2014, cohort 2017, and cohort 2020; (**b**) Treatment steps defined in this study. Following the 2019 GINA guidelines, low-dose budesonide / beclomethasone with formoterol was included as a reliever medication option. Therefore, prescriptions of low-dose budesonide / beclomethasone with formoterol dispensed before 2020 are still categorized as step 3, while those dispensed after 2020 are categorized as step 1.
Abbreviations: SABA, short-acting beta-agonists; LABA, long-acting beta-agonists; ICS, inhaled corticosteroids.

1. Step 1: SABA or low-dose budesonide/beclomethasone plus formoterol, as needed only
2. Step 2: low-dose ICS
3. Step 3: low-dose ICS + LABA other than budesonide/beclomethasone plus formoterol, or medium-dose ICS
4. Step 4: medium- to high-dose ICS + LABA, triple therapy (fixed-dose combination of ICS, LABA, and LAMA), or high-dose ICS only
5. Step 5: medications prescribed by specialists or biologics such as benralizumab.

Tiotropium can be used as an alternative to LABA in case of side-effects. When using montelukast, individuals were assigned to step 3 or a higher step, depending on the additional medication they took. The combination of ICS and LABA could be simultaneous use of separate ICS inhalers and LABA inhalers, or a fixed-dose combination inhaler containing both components. The specific daily dose cut-off values for categorizing each type of ICS, LABA, or their combination

as low, medium, or high doses are included in the Table S2. This criterion does not apply to SABA, as its role is exclusively as a reliever medication, irrespective of its prescribed dosage.

Variables

We considered age at initiation, sex, and chronic medication use as covariates. Covariate data were obtained from the IADB.nl database. Age at initiation was defined as the year difference between the date of birth and the date of initiation. Chronic medication use was defined as having at least two prescriptions for medications related to a single chronic condition (eg diabetes, hypertension, rhinitis, or allergies) within the year prior to the initiation date. The chronic conditions considered and the corresponding medications are detailed in the Table S3).[23–25]

The primary outcomes of interest were time to first treatment switch (further divided into "step up" or "step down") and time to first oral prednisolone/prednisone course. Dispensing of oral prednisone or prednisolone therapy (with a daily dose of 30 to 40 mg for a period of 3 to 7 days, maximum extension of 14 days)[26,27] was used as a proxy of asthma exacerbation. The secondary outcomes of interest were proportion of patients with switch, proportion of patients on oral prednisolone/prednisone, number of switches, number of steps switched, and number of oral prednisolone/prednisone courses.

The time-varying proportion of days covered (tPDC) was calculated for each dispense using the formula below[28] and was used to define each patient's period of use, while not being too strict regarding poor adherence. This algorithm was used and validated in a previous paper.[5] For controller medications, discontinuation was defined as a tPDC of 0.5 or less (for reference: a tPDC of 1 represents full adherence). For reliever medications, full adherence was represented by a tPDC of 0.5, and discontinuation was defined as a tPDC of 0.05 or less. Patients' asthma medication use at different time points was then determined based on tPDC. The detailed explanation of the stepwise analyses can be found in the Supplementary Page 6.

$$\text{tPDC} = \frac{\text{number of dispensed inhalations}/\text{number of daily inhalations}}{\text{interval in days until next dispensing}}$$

Statistical Methods

We summarized the baseline characteristics of initiators in 2014, 2017, and 2020. Descriptive analyses of covariates were performed. Normality of distribution was tested using the Shapiro–Wilk test. Continuous variables were summarized using mean and standard deviation (SD) if normally distributed, or median and interquartile range (IQR) if skewed. Normally distributed continuous variables were compared using an ANOVA test (across three cohorts) and *t*-test (2020 versus 2014/2017), while skewed variables were compared using Kruskal–Wallis test (across three cohorts) and Mann–Whitney *U*-test (2020 versus 2014/2017). Categorical variables were summarized using proportions and compared using chi-square test. Treatment patterns during the two-year follow-up period were also summarized, including the number and proportion of initiators in each treatment step, patients with switch, and patients with oral prednisolone/prednisone course. The number of switches and the number of steps switched were also summarized.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated by Cox proportional hazards model. The difference in time to first switch and in time to first oral prednisolone/prednisone course between the three cohorts was examined using a multivariable Cox regression model, adjusting for age, sex, and chronic drug use that were not evenly distributed among the cohorts (significance threshold: 0.1). Kaplan-Meier survival curves were used to visualize the time to switch and time to prednisolone/prednisone course among initiators in different cohorts. A Log rank test was used to compare the survival curves between groups. To ensure the validity of the survival analyses, individuals included were required to have at least two years of follow-up data after their first dispensing of asthma inhaled medication, thereby minimizing the impact of missing follow-up data. We used negative binomial regression to estimate the incidence rate ratios (IRRs) to compare the rates of oral prednisolone/prednisone courses within 2 years of follow-up between three cohorts, adjusting for age at initiation and sex. A Sankey plot was used to visualize the trajectory of treatment switches across the three cohorts (half-year as interval).

To determine the robustness of the analyses regarding the definition of discontinuation, we performed a sensitivity analysis and set the cut-off value for discontinuation of controller to 0.25 instead of 0.5 for the tPDC-based algorithm, and re-ran the Cox regression and Kaplan-Meier curve analyses.

Analyses were performed using R, version 4.2.1. The significance threshold for all statistical tests was 0.05 (two-tailed).

Results

Study Population

The flow chart in Figure 2 illustrates the patient selection for this study. We identified a total of 9685 individuals who initiated inhaled asthma medications anywhere between 2014 and 2021, based on dispensing records. After excluding possible COPD patients (N = 583) and those not following the index asthma regimens (N = 7), there were a total of 9095 initiators on the index asthma regimens from 2014 to 2021. Specifically, selecting the years 2014, 2017 and 2020, we included 2883 individuals, of which 1193 were in the cohort 2014, 960 in the cohort 2017, and 730 in the cohort 2020.

Population Characteristics

Table 1 summarizes the baseline characteristics of patients in the cohort 2014, 2017, and 2020. In total, 1913 (66.4%) of the 2883 participants were female. The median age at initiation of the population was 32.0 years (IQR: 15.0). In all cohorts, females were more frequently present than males, and the proportion of females was consistent across the three cohorts. There was a significant difference in age at initiation between cohorts, with the 2017 cohort having the lowest median age (30.0 years). However, the median age at initiation during the pandemic did not change significantly compared with the pre-pandemic period (combining 2014 and 2017, $P = 0.298$). Additionally, the prevalence of allergies, rhinitis, and conjunctivitis was lowest in the 2017 cohort compared to the other cohorts, while the other chronic medication use was evenly distributed across the cohorts.

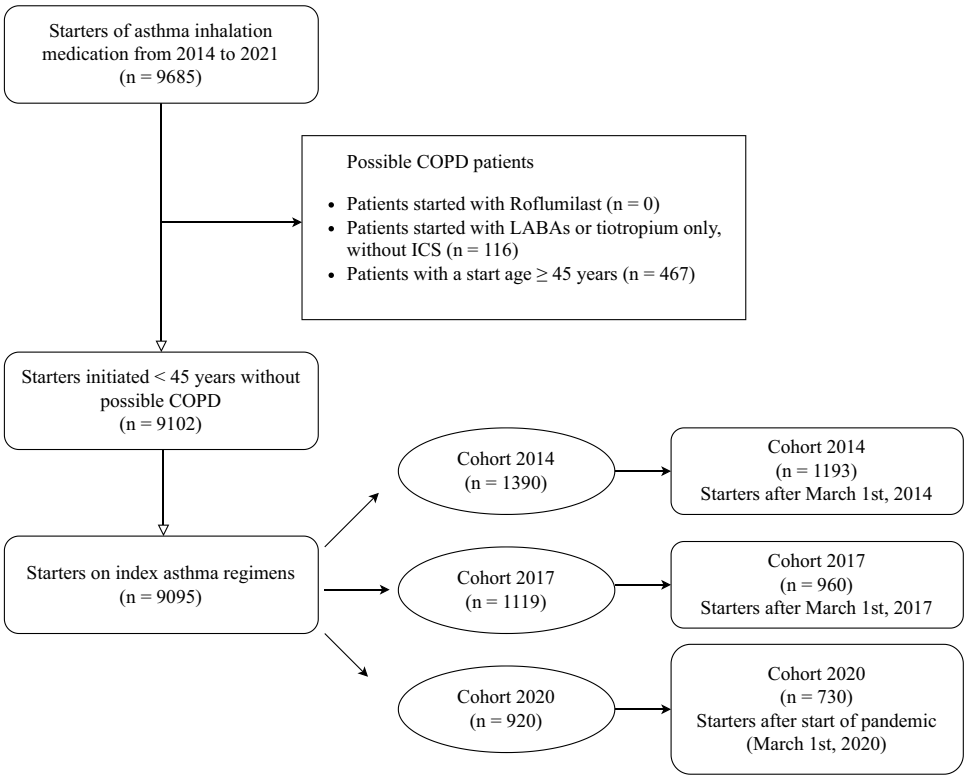

Figure 2 Flow chart of patient selection.

Table 1 Baseline Characteristics of Asthma Medication Initiators in the Study Cohort From 2014, 2017, and 2020 in the Netherlands, Including Demographic and Clinical Variables

	Total	2014[§]	2017[§]	2014/2017	2020[§]	*P* value	
						Overall[¶]	2020 vs 2014/2017[‡]
Number of initiators	2883	1193	960	2153	730		
Sex						0.608	0.594
Male	970 (33.65%)	389 (32.61%)	329 (34.27%)	718 (33.35%)	252 (34.52%)		
Female	1913 (66.35%)	804 (67.39%)	631 (65.73%)	1435 (66.65%)	478 (65.48%)		
Median age at initiation (IQR)	32.00 (15.00)	33.00 (15.00)	30.00 (15.25)	31.00 (16.00)	32.00 (15.00)	< 0.001***	0.298
Age at initiation						0.003**	0.542
16–24 years	804 (27.89%)	305 (25.57%)	299 (31.15%)	604 (28.05%)	200 (27.40%)		
25–34 years	939 (32.57%)	382 (32.02%)	328 (34.17%)	710 (32.98%)	229 (31.37%)		
34–44 years	1140 (39.54%)	506 (42.41%)	333 (34.69%)	839 (38.97%)	301 (41.23%)		
Chronic medication use							
Diabetes	63 (2.19%)	30 (2.51%)	21 (2.19%)	51 (2.37%)	12 (1.64%)	0.448	0.312
Dyslipidemia	61 (2.12%)	28 (2.35%)	23 (2.40%)	51 (2.37%)	10 (1.37%)	0.268	0.141
Obesity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	NA	NA
Hypertension	38 (1.32%)	19 (1.59%)	10 (1.04%)	29 (1.35%)	9 (1.23%)	0.523	0.964
Heart failure	67 (2.32%)	30 (2.51%)	17 (1.77%)	47 (2.18%)	20 (2.74%)	0.360	0.471
Ischemic heart disease	101 (3.50%)	48 (4.02%)	28 (2.92%)	76 (3.53%)	25 (3.42%)	0.378	0.986
Arrhythmia	3 (0.10%)	2 (0.17%)	0 (0.00%)	2 (0.09%)	1 (0.14%)	0.463	1.000
Anxiety	149 (5.17%)	59 (4.95%)	44 (4.58%)	103 (4.78%)	46 (6.30%)	0.259	0.133
Depression	281 (9.75%)	112 (9.39%)	88 (9.17%)	200 (9.29%)	81 (11.10%)	0.358	0.177
Dementia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	NA	NA
Malignancy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	NA	NA
Transplant	8 (0.28%)	5 (0.42%)	2 (0.21%)	7 (0.33%)	1 (0.14%)	0.460	0.669
HIV	3 (0.10%)	1 (0.08%)	1 (0.10%)	2 (0.09%)	1 (0.14%)	0.940	1.000
GORD	310 (10.75%)	124 (10.39%)	108 (11.25%)	232 (10.78%)	78 (10.68%)	0.814	1.000
Osteoporosis	8 (0.28%)	3 (0.25%)	2 (0.21%)	5 (0.23%)	3 (0.41%)	0.717	0.699
Hypothyroid	77 (2.67%)	29 (2.43%)	20 (2.08%)	49 (2.28%)	28 (3.84%)	0.069	0.034*
Arthritis	262 (9.09%)	125 (10.48%)	79 (8.23%)	204 (9.48%)	58 (7.95%)	0.191	0.243
Allergies	606 (21.02%)	265 (22.21%)	176 (18.33%)	441 (20.48%)	165 (22.60%)	0.043*	0.245
Rhinitis	297 (10.30%)	132 (11.06%)	77 (8.02%)	209 (9.71%)	88 (12.05%)	0.014*	0.083

(*Continued*)

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Table 1 (Continued).

	Total	2014[§]	2017[§]	2014/2017	2020[§]	*P* value	
						Overall[¶]	2020 vs 2014/2017[‡]
Conjunctivitis	40 (1.39%)	22 (1.84%)	4 (0.42%)	26 (1.21%)	14 (1.92%)	0.007**	0.217
Dermatitis	143 (4.96%)	54 (4.53%)	46 (4.79%)	100 (4.64%)	43 (5.89%)	0.392	0.215

Notes: [§] Index date after March 1. [¶] Categorical variables were compared using chi-square test, while continuous variables were compared using ANOVA test (if normally distributed) or Kruskal–Wallis test (if skewed). Significance code: 0 "***" 0.001 "**" 0.01 "*" 0.05. [‡] Categorical variables were compared using chi-square test, while continuous variables were compared using independent *t*-test (if normally distributed) or Mann–Whitney *U*-test (if skewed). Significance code: 0 "***"0.001 "**"0.01 "*"0.05.
Abbreviations: IQR, interquartile range; GORD, gastro-oesophageal reflux disease; HIV, human immunodeficiency virus.

Table 2 Treatment Patterns of Asthma Medication Initiators in the 2014, 2017, and 2020 Cohorts During a 2-year Follow-up Period in the Netherlands

	2014[§]	2017[§]	2020[§]	*P* value	
				Overall[¶]	2020 vs 2014/2017[†]
Number of initiators	1193	960	730		
Initial steps (number and percentage)				< 0.001***	< 0.001***
Step 1	601 (50.72%)	521 (54.50%)	453 (62.05%)		
Step 2	59 (4.98%)	55 (5.75%)	42 (5.75%)		
Step 3	229 (19.32%)	159 (16.63%)	42 (5.75%)		
Step 4	182 (15.36%)	113 (11.82%)	84 (11.51%)		
Step 5	114 (9.62%)	108 (11.30%)	109 (14.93%)		
Patients with switch (number and percentage)					
With switching[‡]	602 (50.46%)	472 (49.17%)	341 (46.71%)	0.220	0.117
Step-up	498 (41.74%)	394 (41.04%)	293 (40.14%)	0.716	0.497
Step-down	424 (35.54%)	286 (29.79%)	210 (28.77%)	0.001**	0.031*
Without switching	591 (49.54%)	488 (50.83%)	389 (53.29%)	0.220	0.117
Number of switches					
Median and IQR	1 (IQR = 2)	0 (IQR = 1)	0 (IQR = 1)	0.029*	0.046*
Number of steps switched					
Median and IQR	1 (IQR = 3)	0 (IQR = 3)	0 (IQR = 4)	0.264	0.473
Patients on oral prednisolone / prednisone (number and percentage)				0.008**	0.002**
Yes	264 (22.13%)	220 (22.92%)	125 (17.12%)		
No	929 (77.87%)	740 (77.08%)	605 (82.88%)		

Notes: [§] Index date after March 1. [¶] Categorical variables were compared using chi-square test, while continuous variables were compared using ANOVA test (if normally distributed) or Kruskal–Wallis test (if skewed). Significance code: 0 "***" 0.001 "**" 0.01 "*" 0.05. [†] Categorical variables were compared using chi-square test, while continuous variables were compared using independent *t*-test (if normally distributed) or Mann–Whitney *U*-test (if skewed). Significance code: 0 "***" 0.001 "**" 0.01 "*" 0.05. [‡] "Switching" in this context refers to any switching during the 2-year follow-up period. For example, if a patient ever stepped up and down, then that patient is considered in both the "step-up" and "step-down" categories.
Abbreviation: IQR, interquartile range.

Treatment Patterns

Table 2 presents the treatment patterns observed in the three cohorts over a two-year follow-up period. In general, in all cohorts, more than half of the individuals initiated treatment at step 1. Of note, the 2020 cohort showed a decrease in the proportion of patients at step 3, followed by an increase at step 1 and step 5 compared to the 2014 and 2017. In 2014, 2017, and 2020, there were 50%, 51%, and 53% of people who remained in their original steps and never switched during the 2-year follow-up period, respectively, but the difference was not statistically significant. There was a significant downward trend in the proportion of individuals who stepped down their treatment (35% in 2014, 30% in 2017, and 29% in 2020).

Time to First Treatment Switch

Table S4 and Figures 3 and 4 show the results of Kaplan-Meier survival curves and Cox regression analyses. Among patients who ever switched, the median time to first switch was 103 days in 2014, 102 days in 2017, and 149 days in 2020. After adjustment for age at initiation, sex, and chronic medication use, the hazard ratio for treatment switch in the cohort 2020 was 0.86 (95% CI: 0.76–0.99, $P = 0.032$), a 14% reduction, in comparison to the cohort 2014 (as shown in Figure 3c). Females were more likely to switch than males (aHR: 1.12 (95% CI: 1.00–1.26), $P = 0.042$).

We divided treatment switch into "stepping-up" and "stepping-down" (as shown in Figure 4). Among patients who stepped-up, the median time to first stepping-up was 93.5 days in 2014, 88.5 days in 2017, and 149 days in 2020. The hazards ratio for stepping-up in treatment steps did not show a statistically significant difference between the pre-pandemic and pandemic cohorts (Figure 4a, $P = 0.500$). Among patients who stepped-down, the median time to first

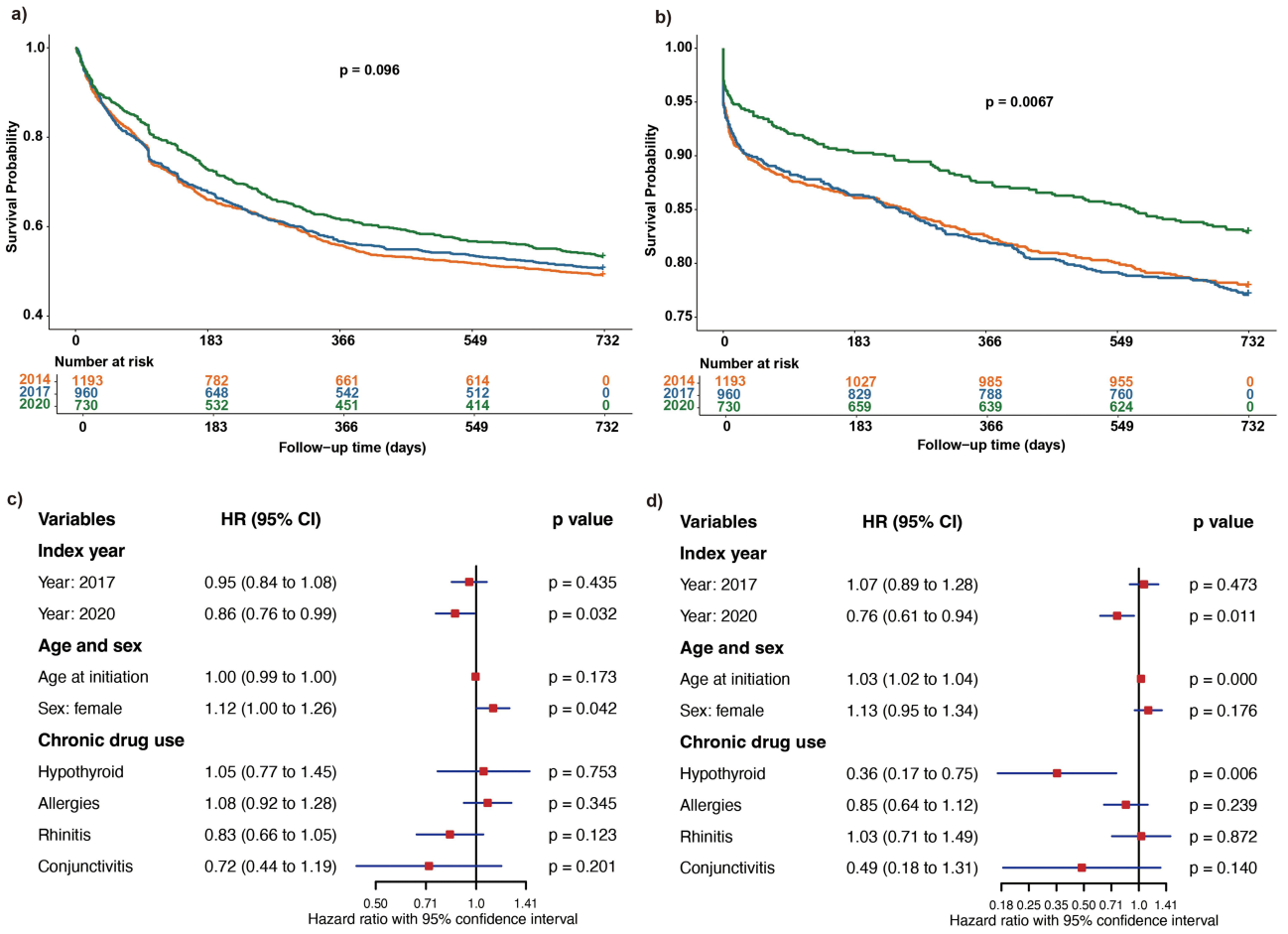

Figure 3 Kaplan-Meier survival curve of (**a**) first treatment step switch and (**b**) first oral prednisolone/prednisone course. Forest plot of the multivariable Cox regression analysis of (**c**) first treatment step switch and (**d**) first oral prednisolone/prednisone course. The independent variable was the calendar year in which patients initiated their inhaled asthma medication. The covariates we adjusted for were age, sex, and chronic medication use (hypothyroid, allergies, rhinitis, conjunctivitis). The orange line represents the cohort 2014, the blue line represents 2017, while the green line represents 2020.

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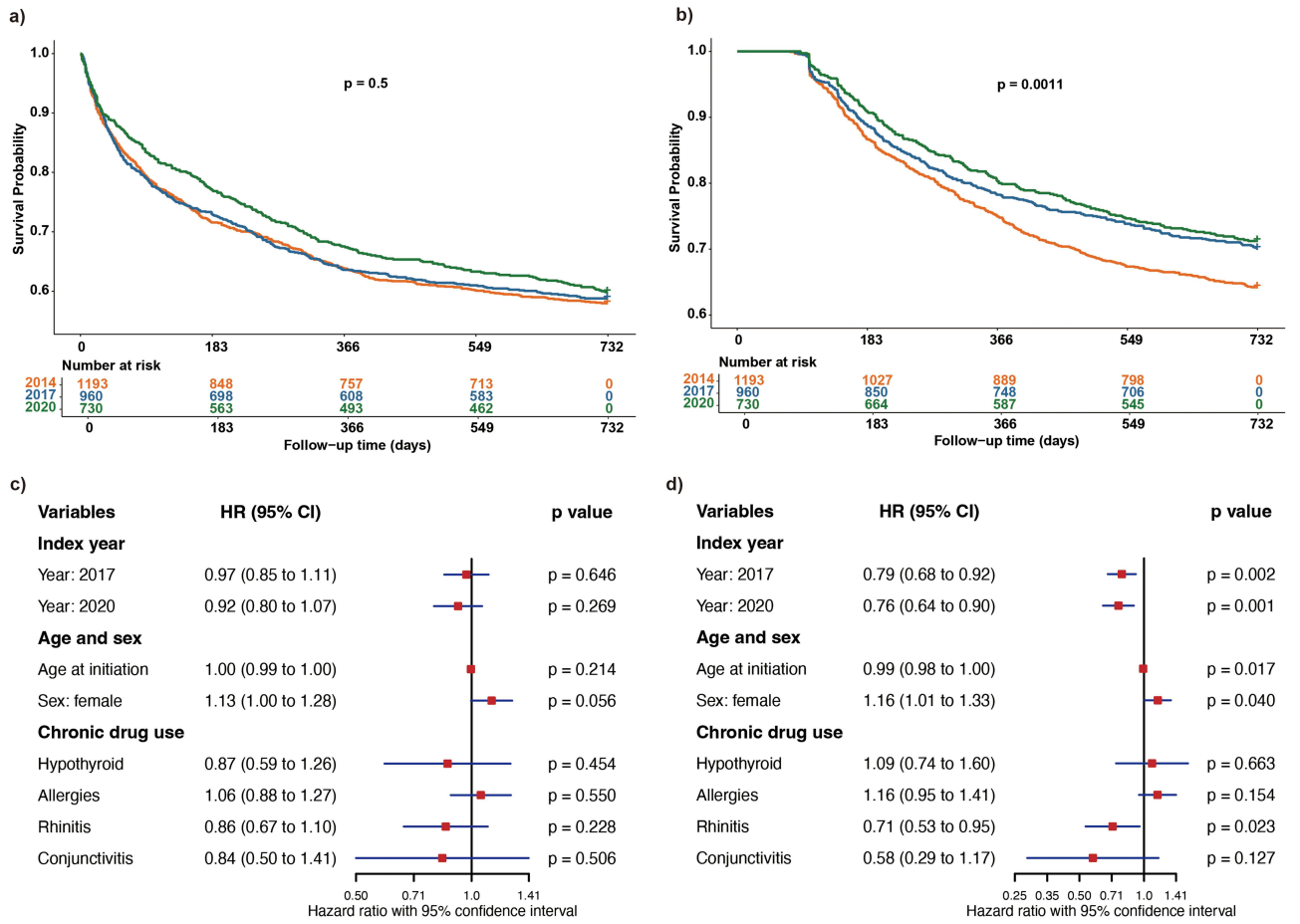

Figure 4 Kaplan-Meier survival curve of (**a**) first stepping-up and (**b**) first stepping-down. Forest plot of the multivariable Cox regression analysis of (**c**) first stepping-up and (**d**) first stepping-down. The independent variable was the calendar year in which patients initiated their inhaled asthma medication. The covariates we adjusted for were age, sex, and chronic medication use (hypothyroid, allergies, rhinitis, conjunctivitis). The orange line represents the cohort 2014, the blue line represents 2017, while the green line represents 2020.

stepping-down was 247 days in 2014, 230 days in 2017, and 262 days in 2020. From 2014 to 2020, there is a general downward trend in the likelihood of stepping-down. The risk for stepping-down was significantly lower by 21% in the cohort 2017 (aHR: 0.79 (95% CI: 0.68–0.92), $P = 0.002$) and 24% in the cohort 2020 (aHR: 0.76 (95% CI: 0.64–0.90), $P = 0.001$) when compared to the cohort 2014.

Time to First Oral Prednisolone/Prednisone Course

Among patients who took oral prednisolone/prednisone, the median time to first oral prednisolone/prednisone course was 55 days in 2014, 88 days in 2017, and 125 days in 2020. There was statistically significant difference in the probability for having an oral prednisolone/prednisone course between cohorts (Figure 3b, $P = 0.007$). The adjusted hazard ratio for oral prednisolone/prednisone course was 0.76 (95% CI: 0.61–0.94, $P = 0.011$), a 24% reduction, comparing the cohort 2020 to 2014 (as shown in Figure 3d). Older patients were more likely to take oral prednisolone/prednisone (aHR: 1.03 (95% CI: 1.02–1.04), $P < 0.001$).

The negative binomial regression analysis (Table S5 and Figure S1) showed significant differences in the number of prednisolone/prednisone courses across the three cohorts. The prednisolone/prednisone courses were less frequent in 2017 and 2020 than in 2014. The average number of prednisolone/prednisone courses was 1.10 in 2014, 0.87 in 2017, and 0.52 in 2020. Compared to the 2014 cohort, the adjusted IRR for the 2017 cohort was 0.85 (95% CI: 0.72–0.99, $P = 0.044$), while the adjusted IRR for the 2020 cohort was 0.48 (95% CI: 0.40–0.58, $P < 0.001$).

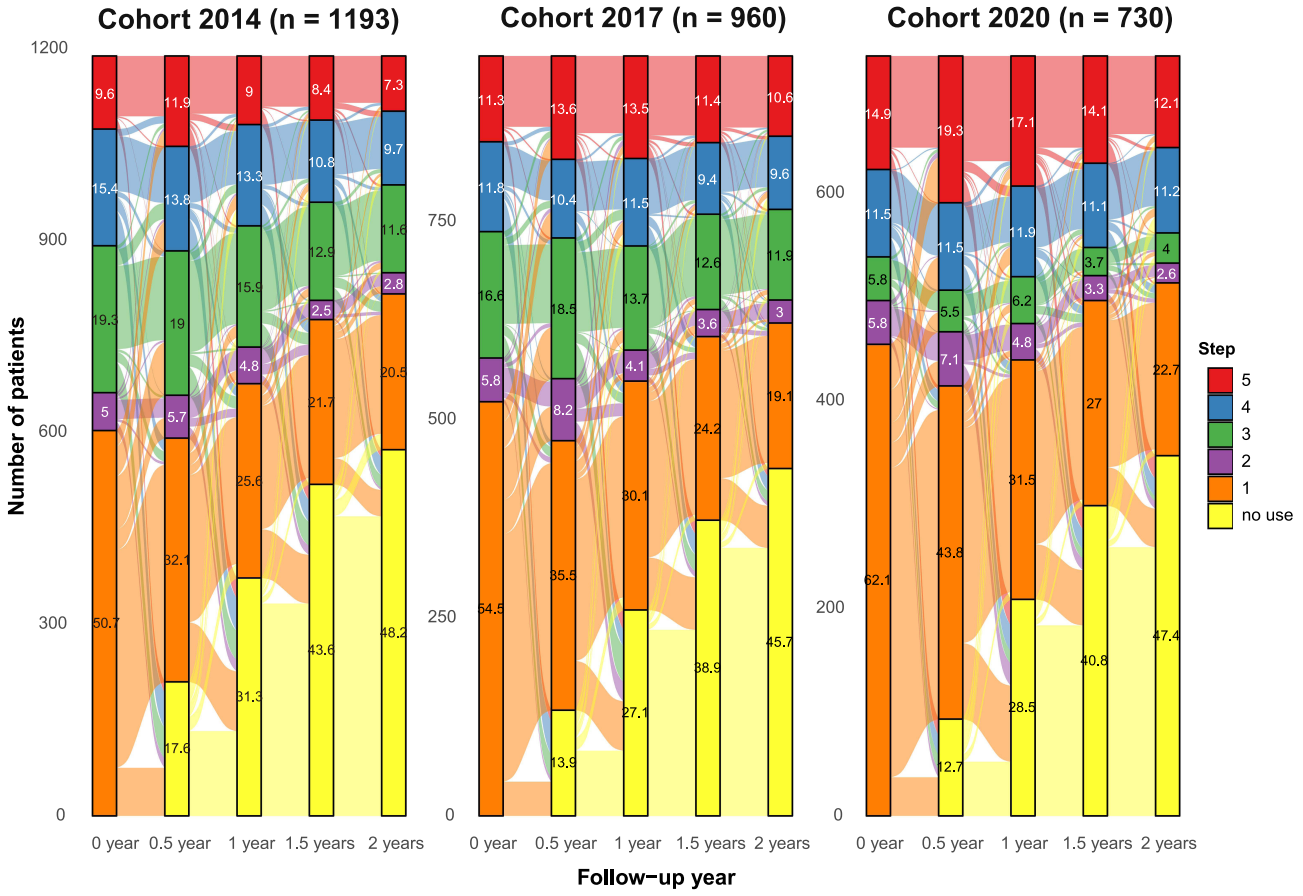

Figure 5 Sankey diagram of treatment step changes within the 2-year follow-up period, with half-year intervals. Each node in the diagram represents a treatment step, and the width of the flow bands between nodes is proportional to the number of patients moving between those treatment steps. The number within each bar represents the proportion of patients at each step at each follow-up time.

Trajectory of Treatment Step Changes

The Sankey diagram in Figure 5 presents the dynamic flow of patients through different treatment steps over a two-year follow-up period in the cohort 2014, 2017, and 2020. Across all cohorts, there were some similar patterns of treatment trajectories observed. In general, the majority of patients remained in the same treatment step between each half-year interval. Approximately 19% of patients who initially started at step 1 either escalated to a higher treatment step (step 2, 3, 4, or 5) or discontinued therapy within the first 6 months. For patients at step 2 to 4, the most common step-down option was directly to step 1. Patients at step 5 were less likely to switch to other steps, and the most common option was to step-down to step 4 or to discontinue therapy.

Comparing the pre-pandemic and pandemic cohorts, the proportion of patients moving from step 1 to step 5 within the first 6 months was higher (Figure 5). The proportion of patients at step 4 decreased over the 2-year follow-up period in the cohort 2014, fluctuated slightly during follow-up in the cohort 2017, and remained stable during follow-up in the cohort 2020. No significant increase in treatment discontinuation was observed during the pandemic period.

Sensitivity Analysis

The sensitivity analysis assessed the robustness of the survival analysis results by lowering the discontinuation cut-off value for controller medication from 0.5 to 0.25 for the tPDC-based algorithm. The hazard ratios associated with the index year remained consistent with those found in the primary analysis. The change in the cut-off value had minimal effect on the direction and magnitude of the results (Table S6 and Figures S2–S4).

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Discussion

In this study, we aimed to determine the impact of the COVID-19 pandemic on differences in dispensing patterns among adults initiating asthma inhalers in the Netherlands. The data showed that more than half of the patients started their asthma treatment at step 1, and more than half of the patients remained on their initial treatment steps throughout the two years of follow-up. We found that fewer asthma patients switched their treatment steps (14% reduction) and took an oral prednisolone/prednisone course (24% reduction) during the pandemic. There was a general downward trend in stepping-down from 2014 onwards, with a 21% reduction in stepping-down in 2017 and a 24% reduction in 2020. Oral prednisolone/prednisone courses were less frequent in 2017 and 2020 than in 2014, with a 15% reduction in 2017 and a 52% reduction in 2020.

In all cohorts, more than half of the patients remained on their initial treatment steps and never switched throughout the study period, while most patients started at step 1 (reliever medication only). This finding is consistent with previous studies. Gayle et al[6] found that more than 78% of children and adults with asthma remained within their treatment step within a 6-month follow-up period, while Mommers et al[5] highlighted the low proportion of step changes in more than 19,000 young adults starting asthma medication in the Netherlands between 1994 and 2021. However, there were some differences in treatment trajectories between cohorts. In 2020, more people started at step 1 or step 5. The increase in step 1 may be related to the decrease in patients starting at or using step 3 during the follow-up, likely due to the 2019 GINA guideline update.[29] This revised guideline introduced low-dose budesonide/beclomethasone plus formoterol as a reliever option. However, our data source, IADB.nl, does not specify whether these medications were used on an as-needed or daily basis. Therefore, we assumed that prescriptions of low-dose budesonide/beclomethasone plus formoterol before 2020 indicated "daily use" (step 3), while those after 2020 reflected "as needed" (step 1). The higher number of people starting treatment at step 5 is likely due to the incidental nature of the asthma diagnosis in this context. Many people were seen by respiratory specialists for COVID-19 infection with symptoms that could be caused by an exacerbation of asthma, such as shortness of breath. During these visits, asthma was often diagnosed as an incidental finding, resulting in more patients starting at step 5. These findings confirm previous research on asthma treatment patterns, while our study provides new insights into how recent guidelines and the pandemic are changing treatment trajectories. A substantial proportion of patients remained on their initial steps could indicate good asthma control without any side effects, or be a result of clinician inertia, either fearing the risk of adverse events by stepping up or fearing uncontrolled asthma by stepping down.[7]

Fewer people switched their treatment in 2020 than in 2014. This was likely due to a reduced likelihood of stepping down, as the risk of stepping up remained stable during the pandemic. These findings align with our initial hypothesis that a smaller proportion of individuals adjust their treatment intensity during the pandemic. This trend was driven by three key factors. First, changes in clinical practice prior to the pandemic played a role, in particular the 2015 NHG guideline recommending the use of spirometry for asthma diagnosis to ensure appropriate treatment initiation.[21] Additionally, increasing evidence in support of stepping down contributed to a significant decline in stepping down as early as 2017.[30] Second, the COVID-19 pandemic limited in-person consultations and monitoring, reducing opportunities for treatment reassessment.[9] Clinicians are more cautious about stepping down, which requires at least 12 weeks of symptom control monitoring.[31,32] Many patients avoided healthcare settings due to pandemic-related anxiety,[33] further discouraging treatment changes. However, step-ups remained stable, as patients with worsening symptoms still sought medical attention to increase treatment intensity. Third, although there is ongoing debate about the bidirectional relationship between asthma and COVID-19, the current consensus emphasizes the importance of medication adherence in asthma patients[34] because poorly controlled asthma may increase the risk of severe COVID-19.[17] Patients with well-controlled asthma are not necessarily more susceptible to SARS-CoV-2 infection.[18] The GINA strategy recommends that asthma patients continue on their usual asthma medications during the COVID-19 pandemic.[34] As a result, it is less likely to step-down treatments in the context of the pandemic.

Patients were 24% less likely to be prescribed an oral prednisolone/prednisone course during the pandemic, and the prescription rate also experience 52% reduction in 2020. This finding is consistent with our initial hypothesis of decreased use of oral corticosteroids and global findings. For example, one study reported a 41.9% decrease in asthma exacerbation rates (hospitalization or emergency department (ED) visit) in the United States (US) from March to December 2020 when compared with pre-pandemic period.[13] Another study in the US also showed a reduction in asthma exacerbations (oral

corticosteroids courses, hospitalization, or ED visit) from 0.264 to 0.214 (18.9% reduction) during the pandemic.[35] These findings highlight the significant impact of pandemic-related changes on asthma exacerbation, such as reduced exposure to viral respiratory infection,[36] which benefited from stay-at-home policies during the pandemic.

Baseline characteristics also influenced asthma treatment patterns. We observed that older patients were less likely to step down and more likely to receive oral prednisolone/prednisone, probably due to an increased likelihood of comorbidities and polypharmacy, as well as worse asthma control and reduced treatment adherence.[37] Female patients were more likely to switch their treatment steps, primarily stepping down, as they tend to perceive and report more frequent and severe symptoms,[38] which may lead to starting at an inappropriate step. Patients with rhinitis were also less likely to step down, as allergic rhinitis is associated with more severe asthma and greater difficulty in controlling asthma symptoms.[39]

To our knowledge, this is the first study to compare asthma treatment trajectories before and during the COVID-19 pandemic with two-year follow-up using a representative and reliable data source from a large dispensing database instead of self-report. The rationale for this cohort design has three advantages. First, we have a comparable follow-up time between cohorts. Second, the robustness of our results is enhanced by using two pre-pandemic reference cohorts for self-comparison. If both pre-pandemic cohorts show comparable trends when compared to the COVID-19 cohort, we can be more confident that the observed effects are not due to random variation. Third, because the pre-pandemic cohorts are from different time periods, we can examine potential temporal trends that may have existed prior to COVID-19. Moreover, the consistency of the results in the sensitivity analysis, even with a lowered controller discontinuation cut-off value, underscores the robustness and reliability of our findings.

We acknowledge some limitations in this study. First, some misclassification may have occurred when excluding patients with possible COPD, as it is challenging to differentiate between asthma and COPD based on dispensing records. Nevertheless, we excluded patients aged 45 years or older at initiation, as asthma tends to present at a younger age compared with COPD. Research on the joint prevalence of asthma and COPD in different age groups indicates that individuals diagnosed with COPD outnumber those with asthma from the age of 45 years.[20] This exclusion criteria could reduce the likelihood of misclassification in our asthma cohort. In addition, we excluded patients using only LABA or tiotropium, as these are commonly prescribed for COPD, but not without ICS for asthma. Therefore, we believe that we have minimized misclassification and excluded possible COPD patients.

Second, the IADB.nl database captures prescription patterns but lacks clinical, behavioral, and contextual data. While we observed changes in asthma treatment trajectories, we could not directly assess potential drivers such as shifts in healthcare access (eg, reduced clinic visits, telemedicine adoption), environmental factors, or public health interventions (eg, prioritization of acute COVID-19 care over chronic disease management).

Third, by using oral corticosteroid prescriptions as a proxy for asthma exacerbations, there is potential for both underestimation and overestimation of asthma exacerbations. On the one hand, since hospital or emergency care dispensing data are not available in our database, we may have missed cases of exacerbations treated in these settings. On the other hand, the broader use of oral corticosteroids beyond asthma care could lead to the inclusion of courses unrelated to asthma exacerbations. However, this definition aligns with recommendations from expert groups, such as Fuhlbrigge et al,[40] who define asthma exacerbations as a worsening of asthma requiring systemic corticosteroids to prevent a serious outcome. Additionally, this definition is a robust and widely used measure to assess asthma exacerbations in real-world settings.[27]

Fourth, the selection of March 1, 2020, as the cutoff date for defining the pandemic cohort may not fully capture the variation in the onset and impact of the COVID-19 pandemic across different countries and populations. The timing of public health measures, lockdowns, and changes in healthcare access differed globally. Additionally, differences in healthcare systems and asthma treatment guidelines across countries may further limit the applicability of our results outside the Netherlands.

Despite limitations, our findings provide clinically relevant insights. Real-world asthma management often involves non-stepwise treatment escalation, which deviates from the GINA step-up guidelines.[32] Based on the findings that step-down strategies can maintain asthma control while reducing costs,[30] they should be advocated in real-world practice. As the rate of oral prednisolone/prednisone decreased in 2017 and 2020, it also reflects improved asthma management over time.

Future research should extend follow-up periods to track long-term treatment trajectories beyond the COVID-19 pandemic, and consider region-specific healthcare contexts to account for variations in asthma management. Linking prescription data to clinical records would help clarify the reasons for the decline in stepping down, while integrating

patient-reported outcomes could provide a clearer picture of asthma control. In addition, investigating the role of telemedicine in asthma care and exploring patient perspectives on medication adherence during the pandemic would provide valuable insights. Understanding how healthcare interactions, such as face-to-face versus telehealth visits, influence treatment decisions is another important area for future studies. Our work lays the groundwork for these investigations and highlights the need for comprehensive research that includes clinical, behavioral, and health system factors to better understand and optimize asthma management.

Conclusion

Our study highlights important changes in asthma treatment trajectories during the COVID-19 pandemic. The observed reduction in switching step (14%) and stepping down (24%) in 2020 may be a result of pandemic-related reductions in routine healthcare visits and guideline-based adherence to initiate with more appropriate steps. The reduction in oral prednisolone/prednisone use (24%) may reflect improved asthma control, possibly related to fewer exacerbations due to reduced viral exposure during the pandemic. A key limitation of this study is its reliance on dispensing data alone, which did not allow us to identify the precise factors underlying the observed trend. Future research should integrate clinical and behavioral data to disentangle the specific contributions of guideline updates, healthcare access, healthcare interactions (face-to-face or telemedicine), and pandemic-related behavioral changes to these declining trends.

Data Sharing Statement

The datasets supporting the conclusions of this article are included within the article and its additional files. Informed consent was not required as no personal information was used in our article. The SQL and R code for data analysis can be shared by emailing the corresponding author.

Ethics Approval and Informed Consent

The University of Groningen IADB.nl community pharmacy dispensing database contains data that is collected in accordance with the Dutch and European guidelines on privacy requirements (GDPR) for handling human data. Approval of the medical ethics committee was not needed nor required for this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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References

1. Abbafati C, Abbas KM, Abbasi-Kangevari M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. 2020;396(10258):1204–1222. doi:10.1016/S0140-6736(20)30925-9
2. Data from the Netherlands by disease: asthma. Available from: www.international-respiratory-coalition.org. Accessed December 31, 2021.

3. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet*. 2018;391(10122):783–800. doi:10.1016/S0140-6736(17)33311-1
4. Global Initiative for Asthma (GINA). 2022 GINA report, global strategy for asthma management and prevention; 2022. Available from: https://ginasthma.org/gina-reports/. Accessed April 03, 2025.
5. Mommers I, van Boven JFM, Schuiling-Veninga CCM, et al. Real-world dispensing patterns of inhalation medication in young adult asthma: an inception cohort study. *Clin Epidemiol*. 2023;15:721–732. doi:10.2147/CLEP.S410036
6. Gayle A, Tebboth A, Pang M, et al. Real-life prescribing of asthmatic treatments in UK general practice over time using 2014 BTS/SIGN steps. *NPJ Prim Care Respir Med*. 2019;29(1):25. doi:10.1038/S41533-019-0137-7
7. Gionfriddo MR, Hagan JB, Rank MA. Why and how to step down chronic asthma drugs. *BMJ*. 2017;359:j4438. doi:10.1136/BMJ.J4438
8. Oreskovic NM, Kinane TB, Aryee E, Kuhlthau KA, Perrin JM. The unexpected risks of COVID-19 on asthma control in children. *J Allergy Clin Immunol Pract*. 2020;8(8):2489–2491. doi:10.1016/J.JAIP.2020.05.027
9. Heins M, Hek K, Hooiveld M, Hendriksen J, Korevaar J. Impact coronapandemie op zorgvraag bij huisartsen (Factsheet A) (impact of the corona pandemic on care demand by general practitioners). *Nivel Accessed*. 2021.
10. Zayen K, Snène H, Blibech H, et al. Asthma management and control during COVID-19 pandemic. *Eur Respir J*. 2021;58:PA970. doi:10.1183/13993003.CONGRESS-2021.PA970
11. Kaye L, Theye B, Smeenk I, Gondalia R, Barrett MA, Stempel DA. Changes in medication adherence among patients with asthma and COPD during the COVID-19 pandemic. *J Allergy Clin Immunol Pract*. 2020;8(7):2384. doi:10.1016/J.JAIP.2020.04.053
12. Dhruve H, D'Ancona G, Holmes S, Dhariwal J, Nanzer AM, Jackson DJ. Prescribing patterns and treatment adherence in patients with asthma during the COVID-19 pandemic. *J Allergy Clin Immunol Pract*. 2022;10(1):100. doi:10.1016/J.JAIP.2021.09.032
13. Lam RW, Inselman JW, Jeffery MM, Maddux JT, Rank MA. National decline in asthma exacerbations in United States during coronavirus disease 2019 pandemic. *Ann Allergy Asthma Immunol*. 2021;127(6):692. doi:10.1016/J.ANAI.2021.09.017
14. De Boer G, Braunstahl GJ, Hendriks R, Tramper-Stranders G. Asthma exacerbation prevalence during the COVID-19 lockdown in a moderate-severe asthma cohort. *BMJ Open Respir Res*. 2021;8(1):e000758. doi:10.1136/BMJRESP-2020-000758
15. Zhou G, De Vos S, Schuiling-Veninga CC, et al. Community use of repurposed drugs before and during COVID-19 pandemic in the Netherlands: an interrupted time-series analysis. *Clin Epidemiol*. 2023;15:923–937. doi:10.2147/CLEP.S418069
16. Taquechel K, Diwadkar AR, Sayed S, et al. Pediatric asthma health care utilization, viral testing, and air pollution changes during the COVID-19 pandemic. *J Allergy Clin Immunol Pract*. 2020;8(10):3378–3387.e11. doi:10.1016/J.JAIP.2020.07.057
17. Doni Jayavelu N, Jackson DJ, Altman MC. Protective mechanisms of allergic asthma in COVID-19. *J Allergy Clin Immunol*. 2023;152(4):873–875. doi:10.1016/J.JACI.2023.08.016
18. Dolby T, Nafilyan V, Morgan A, Kallis C, Sheikh A, Quint JK. Relationship between asthma and severe COVID-19: a national cohort study. *Thorax*. 2023;78(2):120. doi:10.1136/THORAXJNL-2021-218629
19. Visser ST, Schuiling-Veninga CC, Bos JH, De Jong-Van Den Berg LT, Postma MJ. The population-based prescription database IADB.nl: its development, usefulness in outcomes research and challenges. *Expert Rev Pharmacoecon Outcomes Res*. 2013;13(3):285–292. doi:10.1586/ERP.13.20
20. de Marco R, Pesce G, Marcon A, et al. The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle-aged and elderly people from the general population. *PLoS One*. 2013;8(5). doi:10.1371/journal.pone.0062985
21. NHG work group. Dutch college of general practitioners' guideline adults with asthma (third revision).
22. NHG work group. Dutch college of general practitioners' guideline adults with asthma (M27). 2022. Available from: https://richtlijnen.nhg.org/standaarden/astma-bij-volwassenen. Accessed April 03, 2025.
23. Pratt NL, Kerr M, Barratt JD, et al. The validity of the Rx-risk comorbidity index using medicines mapped to the anatomical therapeutic chemical (ATC) classification system. *BMJ Open*. 2018;8(4):e021122. doi:10.1136/BMJOPEN-2017-021122
24. Holvik K, Hjellvik V, Karlstad Ø, et al. Contribution of an extensive medication-based comorbidity index (Rx-Risk) in explaining the excess mortality after Hip fracture in older Norwegians: a NOREPOS cohort study. *BMJ Open*. 2022;12(5):e057823. doi:10.1136/BMJOPEN-2021-057823
25. Daniels B, Tervonen HE, Pearson SA. Identifying incident cancer cases in dispensing claims: a validation study using Australia's repatriation pharmaceutical benefits scheme (PBS) data. *Int J Popul Data Sci*. 2020;5(1):1152. doi:10.23889/ijpds.v5i1.1152
26. Wang Y, Pera V, Boezen HM, et al. Real-world effects of antibiotic treatment on acute COPD exacerbations in outpatients: a cohort study under the PharmLines initiative. *Respiration*. 2022;101(6):553–564. doi:10.1159/000520884
27. Murray CS, Lucas SJ, Blakey J, et al. A real-life comparative effectiveness study into the addition of antibiotics to the management of asthma exacerbations in primary care. *Eur Respir J*. 2021;58(1):2003599. doi:10.1183/13993003.03599-2020
28. Bijlsma MJ, Janssen F, Hak E. Estimating time-varying drug adherence using electronic records: extending the proportion of days covered (PDC) method. *Pharmacoepidemiol Drug Saf*. 2016;25(3):325–332. doi:10.1002/PDS.3935
29. Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management. *Eur Respir J*. 2019;53(6):1901046. doi:10.1183/13993003.01046-2019
30. Rank MA, Liesinger JT, Branda ME, et al. Comparative safety and costs of stepping down asthma medications in patients with controlled asthma. *J Allergy Clin Immunol*. 2016;137(5):1373–1379.e3. doi:10.1016/J.JACI.2015.08.035
31. Thomas A, Lemanske RF, Jackson DJ. Approaches to stepping-up and stepping-down care in asthma. *J Allergy Clin Immunol*. 2011;128(5):915. doi:10.1016/J.JACI.2011.07.014
32. Reddel HK, Bacharier LB, Bateman ED, et al. Global initiative for asthma strategy 2021 executive summary and rationale for key changes. *Am J Respir Crit Care Med*. 2022;205(1):17–35. doi:10.1164/RCCM.202109-2205PP/SUPPL_FILE/DISCLOSURES.PDF
33. Splinter MJ, Velek P, Kamran Ikram M, et al. Prevalence and determinants of healthcare avoidance during the COVID-19 pandemic: a population-based cross-sectional study. *PLoS Med*. 2021;18(11):e1003854. doi:10.1371/JOURNAL.PMED.1003854
34. Global Initiative for Asthma (GINA). GINA guidance about COVID-19 and asthma. 2021. Available from: https://ginasthma.org/wp-content/uploads/2021/03/21_03_30-GINA-COVID-19-and-asthma.pdf. Accessed October 02, 2023.
35. Cvietusa PJ, Goodrich GK, Steiner JF, et al. Transition to virtual asthma care during the COVID-19 pandemic: an observational study. *J Allergy Clin Immunol Pract*. 2022;10(6):1569–1576. doi:10.1016/J.JAIP.2022.02.027
36. Sayed S, Diwadkar AR, Dudley JW, et al. COVID-19 Pandemic-Related reductions in pediatric asthma exacerbations corresponded with an overall decrease in respiratory viral infections. *J Allergy Clin Immunol Pract*. 2022;10(1):91–99.e12. doi:10.1016/J.JAIP.2021.10.067

37. Melani AS. Management of asthma in the elderly patient. *Clin Interv Aging*. 2013;8:913–922. doi:10.2147/CIA.S33609
38. Colombo D, Zagni E, Ferri F, et al. Gender differences in asthma perception and its impact on quality of life: a post hoc analysis of the PROXIMA (patient reported outcomes and xolair® in the management of asthma) study. *Allergy Asthma Clin Immunol*. 2019;15(1):65. doi:10.1186/S13223-019-0380-Z
39. Kritikos V, Price D, Papi A, et al. The burden of self-reported rhinitis and associated risk for exacerbations with moderate-severe asthma in primary care patients. *J Asthma Allergy*. 2020;13:415–428. doi:10.2147/JAA.S266204
40. Fuhlbrigge A, Peden D, Apter AJ, et al. Asthma outcomes: exacerbations. *J Allergy Clin Immunol*. 2012;129(3 Suppl):S34–48. doi:10.1016/J.JACI.2011.12.983