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ORIGINAL RESEARCH

Modelling Asthma Treatment Dynamics: Insights from the g-Formula

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Purpose: The g-formula offers a promising approach to analyze long-term dynamic asthma treatment trajectories. This study investigates whether the g-formula can simulate real-world asthma treatment trajectories and predicts subgroup differences in switching behavior.

Patients and Methods: This retrospective cohort study identified individuals aged 16- to 45 years who initiated inhaled asthma medication in the Netherlands between 1994 and 2021, from the IADB.nl pharmacy dispensing database. We used the g-formula combined with logistic regression to predict treatment trajectories and their associations with various patient characteristics, such as age, sex, chronic drug treatment for atopic diseases (ATD), cardiovascular diseases (CVD), thyroid diseases, arthritis, diabetes, gastroesophageal reflux disease (GERD), mental health problems (MHP), and immunosuppressants.

Results: The simulations predicted 76% of individuals to switch treatment, on average 2.3 times, with the first switch occurring on average after 8.3 months, which agrees with the real-world observations (77%, 2.3 times and 7.9 months, respectively). Fewer 45-year-olds switched treatment compared to 16-year-olds (74% vs 78%, $p < 0.001$), but they switched earlier (8.1 vs 8.6 months, $p < 0.001$) and more frequently (2.4 vs 2.3 times, $p < 0.001$). Women were more likely to switch compared to men. Patients with ATD, CVD, MHP, or GERD switched significantly less often ($p < 0.05$).

Conclusion: The g-formula effectively simulates asthma treatment trajectories and found higher age, male sex, ATD, CVD, MHP, and GERD to decrease overall switching behavior. These patients might benefit from earlier intervention or closer monitoring to reduce delays in treatment progression.

Keywords: asthma, inhaled medication, treatment steps, trajectories, g-formula, prediction

Introduction

Asthma is a chronic disease characterized by inflammation of the lower airways. It expresses itself by recurring exacerbations and symptoms like bronchospasms, dyspnea, mucus hypersecretion, cough, wheezing, and/or tightness of the chest.[1,2] Comorbidities can aggravate asthma, influencing treatment needed to control symptoms or leading to under- or overtreatment when mimicking asthma-like symptoms.[3] For example, features similar to asthma can also occur due to certain medications (eg, aspirin or beta blockers) or due to dysfunctional breathing caused by, eg, cardiovascular disease (CVD) or anxiety, and upper airway inflammation can be influenced by other systemic inflammatory disorders, eg, rheumatoid arthritis, atopic dermatitis, or Graves' disease.[2] The Global Initiative for Asthma (GINA) acknowledges the increased risk of multimorbidity in worsening asthma control, even if only a few asthma symptoms are present, and has developed a stepwise approach for the management of asthma.[4] However, little is known about how the presence of comorbidities affects asthma treatment trajectories in clinical practice. Information on subgroup differences in treatment trajectories, and more specifically, switching between medications, can inform personalized treatment and help to reduce

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treatment delays by identifying those patients who could benefit from earlier intervention and/or closer monitoring. Moreover, further understanding of the impact of certain comorbidities could guide revisions to management guidelines, with a possibility for stratified recommendations for patients with co-existing health conditions. In the long run, optimizing the management of asthma has the potential to reduce healthcare costs by minimizing complications, emergency department visits, and hospitalizations associated with poor asthma control.[5–7] Although some previous studies looked into switches between asthma treatment steps,[8,9] to the best of our knowledge, no other study has looked into switching behavior among comorbidity subgroups of adults initiating general asthma treatment.

Treatment of asthma is a dynamic process, entailing multiple treatment steps with the possibility of switching up and down between these steps based on (lack of) disease control. Adequate statistical machinery is needed to model such dynamic regimes over time.[10] Although the g-formula was developed for counterfactual causal inference in settings of dynamic treatment regimes, its potential goes beyond causal estimation.[10–12] It can produce high-dimensional sets of predictions of an outcome of interest given a set of predictors. In contrast, static regression techniques, such as Cox regression, predict a single outcome over a certain period or at a specific timepoint. The g-formula can utilize regression to predict high-dimensional, longitudinal, treatment trajectories.[13,14] The g-formula allows for effects to cascade over time and correct for time-varying-confounding, by projecting previous predictions onto the next one.[15,16] Other models, like multi-state or decision tree models, may rely on the Markovian assumption, assume that the probability of moving from one state to another is constant over time, or have to deal with exponential growth when the number of discrete states or time points increases.[17] The parametric g-formula is not bound by these assumptions and can more easily deal with high-dimensionality of data, thus offers more flexibility in these regards. Although these assumptions can likely be relaxed using machine learning approaches, such techniques have yet been insufficiently explored by previous research on this topic. Furthermore, the g-formula can provide marginal effect estimates that can be generalized to the population, producing easy-to-interpret results answering "what if?" questions, even in the presence of complex interactions.[11–13] Overall, the parametric g-formula can be used to model dynamic treatment regimes and hence might better approximate real-world asthma treatment trajectories as compared to traditional methods.

This study aims to investigate whether the parametric g-formula could be used to approximate empirical asthma treatment trajectories over time and aims to predict subgroup differences in switching behavior within asthma treatment trajectories.

Materials and Methods

Study Design and Setting

This observational, longitudinal cohort study used dispensing data from community pharmacies in the Netherlands, between January 1st 1994 and December 31st 2021. Follow-up consisted of 720 days from initiation of inhaled asthma medication.

Study Population

Individuals aged between 16 and 45 years old initiating any of the following medications were included:

- short- or long-acting selective β2-adrenoreceptor agonists (SABA/LABA): salbutamol, terbutaline, salmeterol, or formoterol
- inhaled corticosteroids (ICS): beclomethasone, budesonide, fluticasone, or ciclesonide
- fixed-dose combination of ICS and LABA (ICS-LABA): salmeterol-fluticasone, formoterol-budesonide, formoterol-beclomethasone, vilanterol-fluticasone, formoterol-fluticasone, or salmeterol-budesonide.

Individuals had to be present in the dataset at least one year prior and one year posterior to initiation of these drugs and should have received at least one more prescription of the same drug within one year. Individuals who initiated treatment with salmeterol, formoterol, or tiotropium bromide only, or whoever received roflumilast, were excluded (due to high probability of chronic obstructive pulmonary disease (COPD)).

Data Source

This study used the University of Groningen IADB.nl dispensing database.[18] The IADB.nl database includes anonymized patient-level dispensing data from approximately 120 community pharmacies with a total of 1.3 million patients in the north of the Netherlands from January 1st 1994 onwards. Data include sex, date of birth, and dispensing records with dispensing date, Anatomical Therapeutic Chemical (ATC) code, quantity, and prescribed dose. Inclusion in the database is regardless of health insurance status. Due to the high patient-pharmacy commitment in the Netherlands, the dispensing records for each individual in the IADB.nl database are virtually complete, except for medication dispensed during hospitalization and over-the-counter drugs.[18] Of note, over-the-counter sales of asthma inhalation medication were not allowed in the Netherlands during the studied period.

Missingness exclusively concerned the daily dose of ICS and ICS-LABA prescriptions (7% missing) and the number of days for which asthma medication was supplied (10% missing). The daily doses were imputed using the most frequent value, stratified by ATC-code and dose per inhalation. Similarly, missing supply duration was imputed based on the most frequent value, stratified by medication number or, alternatively, by ATC-code, inhaler type (aerosol/powder), and daily inhalations. These imputations were performed before applying a time-dependent proportion of days covered (tPDC)-based algorithm, which proved quite robust in our previous study,[9] and before categorizing daily dosage into low, medium, or high doses, minimizing potential misclassification. Consequently, the impact of missing data on study results is likely negligible.

Outcome Variables

The main outcomes were switches within two years of follow-up, the duration until first switch, and number of switches. We were also interested in whether g-formula simulations for this were in line with empirical observations.

We defined asthma treatment steps (0 to 4) as follows, in accordance with the guidelines for treatment of adult asthma from the Dutch College of General Practitioners (NHG), which follow the Global Initiative for Asthma (GINA) report recommendations:[4,19]

- Step 1: SABA or low-dose ICS + formoterol
- Step 2: Low dose ICS without LABA or long-acting muscarinic antagonist (LAMA)
- Step 3: Medium dose ICS, or low dose ICS plus LABA or LAMA
- Step 4 (and 5): High dose ICS, or medium to high dose ICS plus LABA, triple therapy (ICS plus LABA plus LAMA), or biologics
- Step 0: No current prescriptions meeting any of the criteria of treatment steps 1 to 4

As montelukast is only advised for step 3 or higher, if montelukast was prescribed next to a lower step, this step was updated to step 3 instead. ICS dose was classified into low, medium, or high, based on the total daily dose. The cut-off values were drug and inhaler-specific (Supplement 1). We intended to include step 5 separately, consisting of triple therapy or biologics. However, due to the limited occurrence of these treatments within our study population (<1%), these patients were reclassified into step 4.

A time-dependent proportion of days covered (tPDC)-based algorithm was used to transform the dispensing records into continuous data as described in an earlier study.[9] To limit computation time and memory usage, we only registered the mode of each 30 days, resulting in 24 time periods, with a total follow-up duration of 720 days.

Baseline and Time-Varying Predictors

The included baseline predictors were: year, age, sex, and treatment step at initiation, and presence vs absence of chronic drug treatment for diabetes, CVD, mental health problems, arthritis, thyroid disease, atopic diseases, peptic ulcer and gastroesophageal reflux disease (GERD), and use of immunocompromising medication. Timepoint of follow-up, treatment step at previous time point, and an interaction between these last two were added as time-varying predictors.

Chronic drug treatment for comorbidities was defined as having received at least two dispenses of related medication (for ATC-codes, see Supplement 2) within one year before initiation of asthma treatment.[20,21]

G-Formula

To predict the individual treatment trajectories over time, we utilized parametric micro-simulations with the g-formula.[13,22,23] Stable estimates and confidence intervals were obtained by performing of 25 Monte Carlo simulations within 300 bootstrap iterations.

Model Specification

A set of logistic regression models was fitted within each bootstrap loop of the g-formula,[24] each with a treatment step at time $t+1$ as outcome variable, and included all aforementioned predictors (see Supplement 3 for more information on the models' functional form). Once these models were fitted, we used predictor values observed at the baseline to simulate observations at time point t+1, then used the simulated values at t+1 as input to simulate observations at time point t+2, and so onward until the end of follow-up.

Natural Course Validation

To validate the model, we simulated the natural course in which each patient had their baseline variables set to match the observed data.[13] For this validation, an additional logistic regression model was included in the g-formula to predict censoring. This natural course simulation was compared to the empirical, observed data, guarding against gross model misspecification. The focus of this comparison lies on clinical relevance, as the large sample size of this study may lead to statistically significant results (big data paradox) that might not necessarily be clinically meaningful.

Subgroup Predictions

The subgroups of interest were based on age (16 vs 45 years old), sex and chronic drug treatment for diabetes, CVD, mental health problems, arthritis, thyroid disease, atopic diseases, peptic ulcer and GERD, and immunosuppressants (Supplement 2). To approximate subgroup treatment trajectories, the multinomial logistic regression models in the simulation included interaction terms for the subgroup of interest with timepoint of follow-up, with treatment step at previous timepoint and their interaction. Once fitted, the original data at baseline were used as input in our prediction algorithm, except that first all, and then none of the individuals were set to have the comorbidity (or sex or age) of interest, so each individual appeared in all subgroups. The predicted treatment trajectories were reported and compared with each other to determine the significance of subgroup differences. The individual treatment trajectories were visualized using lasagna plots (Supplement 4).

All analyses were performed using R 4.2.1. The source code is available on GitHub at: https://github.com/IreneMommers/R_gformula_public_2024/.

Results

Patient Selection and Baseline Characteristics

Of the 24,506 included individuals, the majority were female (65%). Chronic drug treatment was most frequently prescribed for atopic disease (22%; includes allergies, allergic rhinitis, conjunctivitis, and dermatitis), followed by mental health problems (14%; includes anxiety, depression, dementia, and sleep disorders), and arthritis (11%). Treatment was mainly initiated in step 1 (51%). The incidence of asthma treatment increased over time, until it peaked in the period 2011–2015 (Table 1). The treatment steps at initiation for each subgroup can be found in Supplement 5.

Observed Data Vs Natural Course Simulation

Observed data showed that many individuals stopped asthma treatment within two years of initiation. After two years, those who continued treatment often found themselves in the same treatment step as at initiation (37%), mainly due to never switching (23%). On average, individuals switched between treatment steps twice, and the first switch occurred

Table 1 Patient and Treatment Characteristics

Total Number of Individuals Included, n	24506
Age, median (IQR)	33 (24–40)
Male sex, n (%)	8563 (35)
Drugs used for comorbidities, n (%)	
Arthritis	2730 (11)
Atopic disease	5446 (22)
Diabetes	404 (1.6)
Cardiovascular disease	1581 (6.5)
Peptic ulcer & GERD	2224 (9.1)
Mental health problems	3497 (14)
Thyroid disease	498 (2.0)
Immunosuppressants	216 (0.9)
Treatment step at initiation, n (%)	
1	12,379 (51)
2	2189 (8.9)
3	4691 (19)
4/5	5247 (21)
Year of initiation, n (%)	
1994–2000	3698 (15)
2001–2005	4335 (18)
2006–2010	4629 (19)
2011–2015	6578 (27)
2016–2020	5266 (21)

Abbreviations: IQR, inter quartile range; n, number; GERD, gastroesophageal reflux disease.

after eight months on average. The observed treatment trajectories (Figure 1A) were closely approximated by the natural course simulation (Figure 1B and Table 2).

Predicted Relation Between Exposures and Treatment Trajectories

Differences in switching behavior were found between subgroups. Individuals aged 45 years were less likely to switch treatment steps compared to those aged 16 years (74.3% vs 78.4%, $p < 0.001$). Those who did switch at older age, switched earlier (8.1 months vs 8.6 months, $p < 0.001$) and more often (2.4 vs 2.3 times, $p < 0.001$) compared to if they had been younger. Females showed a slightly higher switching percentage than males (76.6% vs 75.5%, $p = 0.01$), with no significant difference in time until the first switch. Chronic drug treatment for atopic diseases, CVD, mental health problems, and peptic ulcer and GERD, was predictive for a decreased proportion of switching ($p < 0.001$, $p < 0.001$, $p = 0.003$, and $p < 0.001$, respectively), longer duration until the first switch ($p = 0.03$, $p = 0.04$, $p = 0.003$, and $p = 0.04$, respectively) and sometimes less switches (CVD and mental health problems: both $p = 0.02$). In contrast, chronic drug treatment for arthritis, diabetes, immunosuppressants, and thyroid disease had no significant association with switching behavior (Table 3). Visualizations of the individual treatment trajectories within the subgroups can be found in Supplement 4.

Within the subgroups atopic diseases, CVD, mental health problems or peptic ulcer and GERD, it stands out that individuals are less likely to switch down to a lower treatment step or quit their medication (−4.2%, −3.4%, −1.1%, and −3.5%, as compared to the subgroups without respective chronic drug treatments) and are more likely to end up in the treatment step in which they started (+2.6%,+2.2%, +1.6%, +2.2%, respectively) or step up (+1.7%, +1.2%, −0.4%, +1.4%, respectively). For the subgroup with chronic drug treatment for atopic diseases, the overall number of individuals switching was 74.9% as compared to 76.5%, a difference of 1.6%. Thus, besides less switching, those who did switch were also more likely (~1%) to ultimately switch back to the same treatment step they started in. For the subgroup with chronic drug treatment for CVD compared to without, the opposite seems to be true. Although fewer individuals

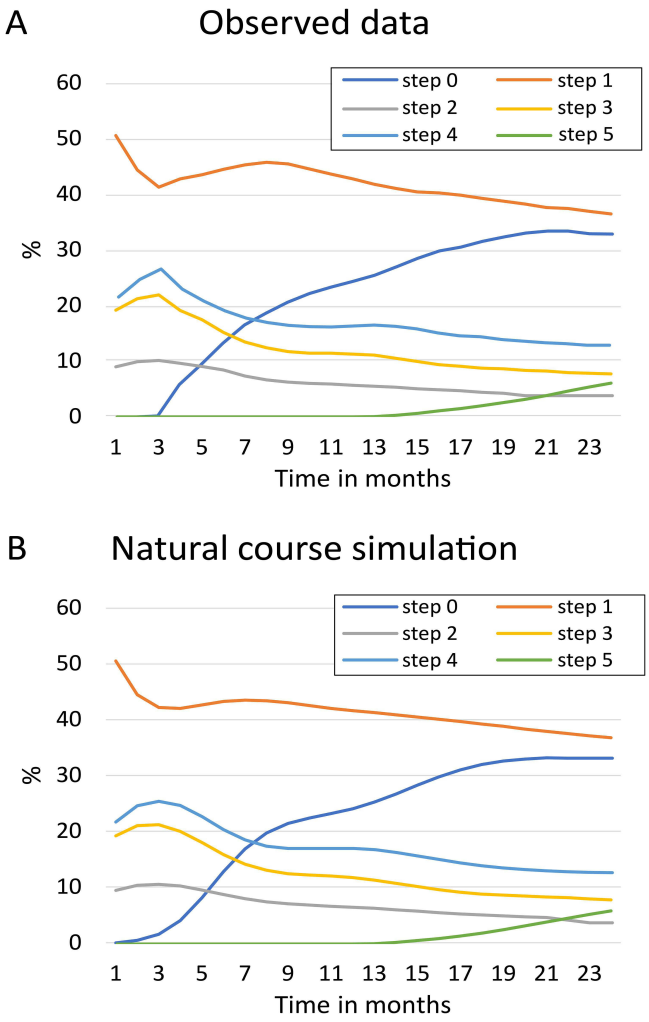

Figure 1 Distributions of individuals across treatment steps over time according to the observed data (**A**) versus the natural course simulations (**B**).

switched their medication (−3.9%; 72.7% vs 76.4%), only +2.2% were found in the same step both at the end and beginning of follow-up, indicating that a relatively lower amount switched back to their previous step after first switching away, with as compared to without chronic medication for CVD. For the subgroups with chronic medication for mental health problems or for GERD, the differences in the proportion of individuals switching (74.8% with, versus 76.4% without chronic medication for mental health problems; 76.4% with versus 74.1% without GERD) are in line with the difference in individuals found in the same treatment step at the beginning and end of follow-up (Table 3 and Supplement 6).

Discussion

In this real-world drug utilization study, we found that natural course simulations using the parametric g-formula were successful in approximating empirical asthma treatment trajectories. We identified differences in switching behavior across subgroups defined by age, sex, and chronic drug treatments. Individuals with chronic drug treatment for atopic diseases, CVD, peptic-ulcer and GERD, or mental health problems switched asthma medication less and/or later.

Some questions might arise due to the choice for dynamic models over traditional static regression models. The longitudinal parametric g-formula allowed us to keep the distribution of all variables at baseline equal to those in the target population, except for the ones of interest. By changing the value of a predictor at baseline and modelling the effect of all variables at time t onto time t+1, a simple change at baseline can cascade across all time points. This allows for easy comparison of full treatment trajectories resulting from different baseline characteristics and enables more detailed

Table 2 Observed Data Versus Natural Course Simulation

	Empirical Data		**Natural Course Simulation**	
Individuals switching, n (%)	18,842 (76.9)		18,621 (76.0)	
Months till first switch, mean (SD)	7.9 (5.4)		8.3 (5.5)	
Number of switches, mean (SD)	2.3 (1.3)		2.3 (1.3)	
First to last step proportions (within start-step %)				
Observed data				
	First Step			
Last step↓	**Step 1**	**Step 2**	**Step 3**	**Step 4**
Step 0	24.9	37.7	43.1	42.8
Step 1	51.7	25.9	22.4	17.5
Step 2	2.8	17.5	2.7	1.1
Step 3	5.4	6.2	19.0	3.7
Step 4	8.5	6.4	8.5	28.5
Censored	6.6	6.3	4.3	6.4
Natural Course Simulation				
	First Step			
Last Step↓	**Step 1**	**Step 2**	**Step 3**	**Step 4**
Step 0	22.6	40.0	45.0	45.5
Step 1	53.4	24.0	21.0	16.6
Step 2	3.4	17.3	2.6	1.0
Step 3	5.4	5.8	19.5	3.3
Step 4	8.5	6.7	7.5	28.3
Censored	6.8	6.2	4.3	5.3

Abbreviations: n, number; SD, Standard deviation.

investigation through the use of, eg, transition matrices or lasagna plots. Although these methods are in line with those used for causal inference, the focus of this study was solely to predict. Therefore, the results should be interpreted predictively rather than causally, especially since we were not able to include all relevant confounders. Nevertheless, by projecting counterfactual scenarios on the entire study population, these methods do allow us to eliminate the influence of differences in the distributions of baseline variables that characterize each subgroup, and thereby to gain more insight into the associations between individual predictors and outcomes of interest along the entire treatment trajectory. This methodology shows potential for application in policy- and decision-making, by predicting the impact of new guidelines, interventions or treatments on the overall population or within specific patient subgroups, or even for informing resource allocation.

The main advantages of the g-formula include its flexibility and dynamic nature. Unlike multi-state models with a limited number of states, the g-formula allows incorporation of as many states as naturally arise from the parameterization (including continuous predictors). Furthermore, employing probabilistic simulations results in less information loss as compared to traditional regression analyses, as full distributions of outcomes are obtained, rather than just the single most likely ones. Additionally, the g-formula overcomes the noncollapsibility problem that is found in many regression analyses.[25,26] Lastly, the dynamic g-formula allows multiple interactions while producing output that remains easy to interpret. Nevertheless, it is important to note that the g-formula is highly computationally intensive, making it most useful when an entire trajectory is of interest, rather than just a single outcome.

Our research results provide insight into how certain comorbidities influence the switching behavior of asthma medications. Individuals with chronic drug treatment for atopic diseases, CVD, mental health problems, and GERD

Table 3 Subgroup Differences in Switching Patterns

	Individuals Switching		Months Until First Switch[a]		Number of Switches[b]	
Altered Condition	**Percentage (95% CI)**	**P-value**	**Mean (95% CI)**	**P-value**	**Mean (95% CI)**	**P-value**
Age						
16 years	78.4 (77.5–79.4)		8.6 (8.5–8.7)		2.2 (2.2–2.3)	
45 years	74.3 (73.3–75.5)	<0.001	8.1 (8.0–8.3)	<0.001	2.4 (2.3–2.4)	<0.001
Sex						
Female	76.6 (76.0–77.1)		8.4 (8.4–8.5)		2.3 (2.3–2.3)	
Male	75.5 (74.7–76.2)	0.01	8.4 (8.3–8.5)	0.79	2.3 (2.2–2.3)	0.01
Arthritis						
Absent	76.2 (75.8–76.7)		8.4 (8.4–8.5)		2.3 (2.3–2.3)	
Present	75.5 (74.2–76.8)	0.28	8.4 (8.3–8.6)	0.79	2.3 (2.2–2.3)	0.20
Atopic diseases						
Absent	76.5 (76.0–77.0)		8.4 (8.3–8.5)		2.3 (2.3–2.3)	
Present	74.9 (74.0–75.9)	<0.001	8.5 (8.4–8.7)	0.03	2.3 (2.3–2.4)	0.56
Cardiovascular diseases						
Absent	76.4 (76.0–76.9)		8.4 (8.4–8.5)		2.3 (2.3–2.3)	
Present	72.7 (70.8–74.5)	<0.001	8.7 (8.4–8.9)	0.04	2.2 (2.2–2.3)	0.02
Diabetes						
Absent	76.1 (75.7–76.6)		8.4 (8.4–8.5)		2.3 (2.3–2.3)	
Present	77.9 (74.7–81.5)	0.26	8.5 (8.1–8.9)	0.75	2.3 (2.2–2.5)	0.67
Immunosuppressants						
Absent	67.2 (75.8–76.6)		8.4 (8.4–8.5)		2.3 (2.3–2.3)	
Present	75.1 (70.1–79.7)	0.60	8.4 (7.8–8.9)	0.94	2.2 (2.0–2.3)	0.17
Mental health problems						
Absent	76.4 (76.0–76.9)		8.4 (8.3–8.5)		2.3 (2.3–2.3)	
Present	74.8 (73.6–76.0)	0.003	8.6 (8.5–8.8)	0.003	2.3 (2.2–2.3)	0.02
Peptic ulcer and GERD						
Absent	76.4 (75.9–76.8)		8.4 (8.3–8.5)		2.3 (2.3–2.3)	
Present	74.1 (72.5–75.6)	<0.001	8.6 (8.5–8.9)	0.04	2.2 (2.2–2.3)	0.05
Thyroid disease						
Absent	76.2 (75.7–76.7)		8.4 (8.4–8.5)		2.3 (2.3–2.3)	
Present	75.9 (72.8–79.2)	0.90	8.6 (8.2–9.0)	0.50	2.3 (2.2–2.4)	0.95

Notes: [a,b]Calculations only included individuals switching.
Abbreviations: CI, confidence interval; GERD, gastroesophageal reflux disease.

switched their asthma medications less frequently, and later compared to those without chronic drug treatment for said comorbidities. Possibly, treating physicians may be more hesitant to decrease asthma medication in patients with multiple conditions, even if asthma symptoms would allow for it, or individuals with chronic drug treatment for these comorbidities may present with more difficult-to-treat asthma symptoms, requiring them to remain on high-dose ICS medication for longer periods. The connection between these comorbidities and asthma is well established in literature: atopic diseases like atopic dermatitis and allergic rhinitis are related to the same IgE-mediated immune response as allergic asthma. These conditions often co-exist and influence each other's development.[27,28] CVD is associated with increased levels of mast cells, eosinophils, inflammatory cytokines, and IgE, suggesting, suggesting a shared pathogenic pathway with asthma.[29] For asthma patients with GERD, there are increased odds of suffering from exacerbations, which may be due to pulmonary inflammation or due to bronchoconstriction caused by vagal nerve stimulation, both induced by reflux.[30,31] In summary, the presence of comorbidities, such as atopic diseases, CVD, mental health problems, and GERD, can impact switching behavior within asthma treatment, likely due to the complex interplay between these conditions and asthma pathophysiology. Further research should focus on understanding the origin of these differences and exploring how they can inform personalized treatment strategies, improve adherence, and

influence long-term outcomes. The results also highlight the complex relationship between mental health problems and asthma medication-switching behavior. Individuals with chronic drug treatment for mental health problems were less likely to either step up or step down their asthma treatment and thus were more likely to remain on the same medication step over time. This switching behavior was not only deviating from those without chronic drug treatment for mental health problems but also from other comorbidities. Previous studies have found that depression and anxiety can result in more severe asthma symptoms and poorer control,[32–34] non-adherence to asthma medication,[35,36] increased health service usage,[37] and a decreased quality of life.[34] Perception of worse asthma control in those with anxiety, as well as hyperventilation, can result in misinterpretation of symptoms as asthma or even induce and worsen asthma attacks, preventing individuals from stepping down their asthma treatment.[32,38] On the other hand, proper treatment of depressive symptoms may improve asthma outcomes, which could prevent the stepping up of asthma treatment.[39,40]

Besides its methodology, the strength of this study lies in the use of a large, real-life dispensing database, the IADB. The individual-level dispensing data is proven to be virtually complete, except for over-the-counter drugs and hospitalizations.[18] The dispensing rates from this database have been found to be representative of the entire Dutch population.[41] However, several limitations should be noted. Due to the nature of the data, no diagnostic information was available, meaning that we had to use dispensed medication as a proxy for disease, which may result in possible misclassification. In addition, the analyses did not include step 5 separately (represented by triple therapy and/or biologics), because of the frequency of this step (n=17 at start and reached by less than 1% of patients ever during the study period) seemed too low to accurately predict the switching behavior to and from step 5. However, with larger sample sizes, incorporation of step 5 could potentially lead to stronger results, as these individuals with severe, uncontrolled asthma might show even more distinct switching behavior. Furthermore, baseline variables were kept constant to prevent confounding, as this study focused only on switching behavior after treatment initiation. Thus, even if no difference was found between subgroups, their real-world baseline characteristics may differ (eg, the treatment steps at baseline differed; Supplement 5). In particular, potential differences in treatment steps at baseline make it challenging to define more precise clinical implications or personalized treatment strategies for patients with specific comorbidities, highlighting a need for further research. However, the presence of differences in switching behavior itself do indicate that earlier intervention and closer monitoring might be of added value. In addition, there can be large differences between scenarios within individuals, even if they were not found for the general population on average. As the focus of this study was to apply the g-formula to predict treatment trajectories at the population level, further research would be needed if this method were to be applied for making predictions on the individual level. Although some relative differences found in this study might appear small, they do represent large numbers of individuals, as asthma is a common chronic disease among young adults.

Conclusion

The parametric g-formula closely approximated the empirical distribution of treatment trajectories in general and within subgroups. The dynamic g-formula provides a good alternative to regression analyses when analyzing processes of a dynamic nature or when interested in full trajectories and shows potential for application in policy- and decision-making, by predicting the impact of new guidelines, interventions or treatments in the full population or within subgroups. This study revealed that higher age, male sex, and chronic drug treatment for atopic disease, CVD, mental health problems, and peptic ulcer and gastroesophageal reflux disease decreased overall switching behavior, indicating that these patients might benefit from earlier intervention or closer monitoring to reduce delays in treatment progression.

Abbreviations

ATC, Anatomical Therapeutic Chemical; ATD, atopic disease(s); COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease(s); GERD, gastroesophageal reflux disease; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting selective β2-adrenoreceptor agonist; LAMA, long-acting muscarinic antagonist;

MHP, mental health problems; NHG, Dutch College of General Practitioners; SABA, short-acting selective β2-adrenoreceptor agonist; tPDC, time-varying proportion of days covered.

Data Sharing Statement

The dataset used for this study was provided by the University of Groningen IADB.nl dispensing database. The data will be accessible via the IADB (email: info@iadb.nl) upon reasonable request. The source code will be made available through GitHub.

Ethics Approval and Informed Consent

The IADB.nl data is processed in accordance with the Dutch and European guidelines on privacy requirements (GDPR) for handling human data.[42] Approval of the medical ethics committee is not needed nor required for research using anonymous medical records, as individuals are not subjected to any actions or rules of conduct.

Consent for Publication

No images or recordings were included in this manuscript that require consent for publication.

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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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