**Appendix 1. List of asthma-related medications used for asthma case definition and the assessment of asthma severity.**

| Medication categories | Medication type | Active ingredient(s) | ATC | DIN | Used in case definition? |
|---|---|---|---|---|---|
| Inhaled corticosteroids (ICS) | Controller | Beclomethasone | R03BA01 | 2242030, 2242029, 374407, 828521, 828548, 872334, 893633, 897353, 1949993, 1950002, 2079976, 2213710, 2213729, 2215039, 2215047, 2215055, 2216531 | Y |
| | | Budesonide | R03BA02 | 2229099, 1978918, 1978926, 852074, 851752, 851760 | Y |
| | | Fluticasone | R03BA05 | 2237247, 2237246, 2237245, 2237244, 2244293, 2244292, 2244291, 2174731, 2174758, 2174766, 2174774, 2213583, 2213591, 2213605, 2213613 | Y |
| | | Ciclesonide | R03BA08 | 2285614, 2285606, 2303671 | Y |
| Short-acting beta-agonists (SABA) | Reliever | Salbutamol | R03AC02 | 790419, 812463, 832758, 832766, 851841, 860808, 867179, 897345, 1926934, 1938851, 1938878, 1945203, 1947222, 1986864, 2022125, 2046741, 2048760, 2069571, 2084333, 2148617, 2154412, 2173360, 2208229, 2208237, 2208245 2212315, 2212323, 2213400, 2213419, 2213427, 2213478, 2213486, 2214997, 2215004, 2215616, 2215624, 2215632, 2216949, 2231430, 2231488, 2231678, 2231783, 2231784, 2232570, 2232987, 2236931, 2236932, 2236933, 2239365, 2239366, 2241497, 2243115, 2243828, 2244914, 2245669, 2259583, 2326450 | Y |
| | | | R03CC02 | 620955, 620963, 874086, 894249, 894257, 1932691, 2035421, 2063689, 2091186, 2146843, 2146851, 2164434, 2164442, 2165368, 2165376, 2212390, 2213435, 2213443, 2213451, 2261324 | Y |
| | | Terbutaline | R03AC03 | 786616 | Y |
| | | Orciprenaline | R03CB03 | 249920, 3891, 2236783, 2229862, 2152568, 2192675 | Y |
| Long-acting beta-agonists (LABA) | Controller | Salmeterol | R03AC12 | 2211742, 2214261, 2231129, 2136139, 2136147 | Y |
| | | Formoterol | R03AC13 | 2230898, 2237224, 2237225 | Y |
| ICS and LABA in combination (ICS+LABA) | Controller | Budesonide, formoterol | R03AK07 | 2245385, 2245386 | Y |
| | | Fluticasone, salmeterol | R03AK06 | 2240835, 2245126, 2245127, 2240836, 2240837 | Y |
| Leukotriene receptor antagonists (LTRA) | Controller | Montelukast | R03DC03 | 2247997, 2238217, 2243602, 2238216 | Y |
| | | Zafirlukast | R03DC01 | 2236606 | Y |
| Anti- | Controller | Omalizumab | R03DX05 | 2260565 | Y |

| | | | | | |
|---|---|---|---|---|---|
| immunoglobulin E monoclonal antibody | | | | | |
| Inhaled mast cell stabilizers | Controller | Cromoglicic acid (cromolyn) | R03BC01 | 2231431, 2231671, 2046113, 534609, 555649, 261238, 638641, 2049082, 2219468 | Y |
| Theophylline | Controller | Choline theophyllinate | R03DA02 | 346071, 405310, 441724, 441732, 451282, 458708, 458716, 476366, 476390, 476412, 503436, 511692, 536709, 565377, 589942, 589950, 792934 | Y |
| | | Theophylline | R03DA04 | 156701, 261203, 460982, 460990, 461008, 466409, 488070, 532223, 556742, 575151, 599905, 627410, 631698, 631701, 692689, 692697, 692700, 722065, 1926586, 1926594, 1926608, 1926616, 1926640, 1966219, 1966227, 1966235, 1966243, 1966251, 1966278, 1966286, 2014165, 2014181, 2230085, 2230086, 2230087 | Y |
| | | Aminophylline | R03DA05 | 14923, 178497, 497193, 497193, 497207, 582654, 582662, 868450, 2014270, 2014289 | Y |
| Inhaled anticholinergics | Reliever | Ipratropium bromide | R01AX03 | 2246084, 2246083, 2163705, 2163713, 2240508, 2240072 | N |
| | | | R03BB01 | 2126222, 2243827, 2231494, 731439, 576158, 2247686, 824216, 2026759, 1950681, 2239131, 2216221, 2210479, 2231785, 2236934, 2236935, 2237134, 2237135, 2239627, 2231135, 2231136, 2231245, 2231244, 2097141, 2097176, 2097168 | N |
| | | Ipratropium bromide, fenoterol | R03AK03 | 02148633 | N |
| | | Tiotropium bromide | R03BB04 | 02246793 | N |
| Other beta-agonists | Reliever | Epinephrine | R03AA01 | 2017555, 466417, 525103, 1927582 | N |
| | | Ephedrine | R03CA02 | 2237085, 2229698, 2100231, 2100258, 2243148, 2236722, 2229678, 2219743, 2012111, 2229711, 38121, 2242961, 876534, 893323, 893331, 438847, 2242639, 2126419, 2126400 | N |
| | | Isoprenaline | R03AB02 | 2017652 | N |
| | | Orciprenaline | R03AB03 | 1923870, 1928449, 2017660, 254134, 3859 | N |
| Other corticosteroids | Controller | Cortisone | H02AB10 | 280437, 16241, 16446, 16438 | N |
| | | Triamcinolone | H02AB08 | 2194090, 15016, 15024, 2194082 | N |
| | | Prednisone | H02AB07 | 610623, 598194, 550957, 312770, 252417, 210188, 868426, 868434, 868442, 21695, 232378, 607517, 508586, 156876, 271373, 271381 | N |
| | | Prednisolone | H02AB06 | 21679, 2230619, 2152541, 2245532 | N |
| | | Methylprednisolone | H02AB04 | 1934325, 1934333, 1934341, 30759, 30767, 36129, 30988, 2245406, 2245400, 2245408, 2245407, 2241229, 2231893, 2231894, 2231895, | N |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 2232750, 2232748, 2063727, 2063697, 2063719, 2063700, 36137, 2230210, 2230211, 30678, 30651, 30643 | |
| | | Betamethasone | H02AB01 | 2237835, 36366, 2063190, 176834, 28096, 28185 | N |
| | | Hydrocortisone | H02AB09 | 888222, 888230, 888206, 888214, 30910, 30929, 872520, 872539, 878618, 878626, 30635, 30600, 30619, 30627 | N |
| | | Dexamathasone | H02AB02 | 2261081, 2250055, 213624, 16462, 354309, 716715, 874582, 1977547, 664227, 2204274, 2204266, 295094, 285471, 489158, 2239534, 732893, 732885, 2260301, 2237044, 2260298, 2237046, 2237045, 1946897, 1964976, 1964968, 1964070, 2279363, 783900, 751863, 2311267, 2240687, 2240685, 2240684 | N |
| Other xanthines | Controller | Theophylline, combination | R03DA54 | 545090, 476374, 334510, 356123, 792942, 721301, 317225, 828718, 640093, 828726, 828742, 307548 | N |
| Other anti-allergic agents | Anti-allergic | Levocabastine | R01AC02 | 2020017 | N |
| | | Ketotifen | R06AX17 | 2221330, 2176084, 2230730, 2218305, 2231680, 2231679, 600784, 577308 | N |

## Appendix 2. Detailed explanation of the partial proportional odds regression and its associated multi-state Markov model

### Overview

Let $Y_{i,t}$ be asthma severity or death in year $t$ from the beginning of follow-up for the $i$th patient in the cohort, where $i$=1, 2 ,…, $n$ and $t$=-2,-1, 0 ,1,…, $n_i$ . $Y_{i,t}$ is classified in to 4 possible states: mild ($Y_{i,t}$ =0), moderate ($Y_{i,t}$ =1), severe ($Y_{i,t}$ =2) and death ($Y_{i,t}$ =3). The partial proportional odds model associated covariates to the probability of observing a given future severity, Pr($Y_{i,t+1}$). Covariates consisted of the history of asthma severity as well as variables of interest (age, sex, socioeconomic status (SES), comorbidity, proportion of days covered [PDC] by asthma controller therapies, all measured in the index year, as well as the calendar year of the index year). The negative time indices indicate the years prior to the index year.

### Empirical model

The reason for including asthma history in the model was to capture the auto-correlative nature of asthma progression (as future severity can depend on the realized past history of severity), thus enabling valid projections of asthma trajectories. The full history at year t can be represented by ($\mathbf{H_{i,t}}$=$\{Y_{i,-2}$ , $Y_{i,-1}$ , $Y_{i,0}$ , $Y_{i,1}$ … , $Y_{i,t}\}$). Because the vector representing asthma history grows with each year of follow-up, a naïve incorporation of asthma history in the regression analysis of this approach requires different regression models for each year of follow-up, with potentially different regression coefficients, thus making the interpretation of the effect of early risk factors on the course of the disease difficult.

Instead, our approach was to create a regression model with Markov (memory-less) property, which replaced the variable of full asthma history with a reduced history variable, $\mathbf{H^c_{i,t}}=\{Y_{i,t-c}, \ldots, Y_{i,t}\}$. In this model, future severity is forecasted by current severity and severity in a fixed past *c* years (c<t), rather than severity in the entire past t years. In this case, because $\mathbf{H^c_{i,t}}$ has similar size and structure for all years, one regression model could be fitted to whole data. A key assumption of this Markov model requires that conditional on this reduced history, the future trajectory is independent of the rest of the history, i.e., $P(Y_{i,t+1}|\ \mathbf{H^c_{i,t}}) \perp\!\!\!\perp \mathbf{H_{i,t-c-1}}$.

In order to choose the appropriate years of severity history that satisfy this Markov property, we started from c=0, i.e., $\mathbf{H^c_{i,t}}=\{Y_{i,t}\}$, and checked whether regression residuals were still correlated with history in the year before the tested history , i.e., $Y_{i,t-1}$. Once conditional independence was achieved, the corresponding history vector $\mathbf{H^c_{i,t}}$ would be chosen for the model. Our results showed that conditional on severity history in the past three years, i.e., $\mathbf{H^c_{i,t}}=\{Y_{i,t-2}, Y_{i,t-1}, Y_{i,t}\}$, a patient with both mild and moderate asthma in the year preceding the past three years, i.e., $Y_{i,t-3}$, had a similar likelihood of transition to severe asthma in the future year (see Appendix 6 for regression results for inclusion of severity history in the past 4 years, together with all other covariates in the main regression model). Therefore, we considered conditional independence as achieved when we included severity history in the past three years, i.e., c=2, $\mathbf{H^c_{i,t}}=\{Y_{i,t-2}, Y_{i,t-1}, Y_{i,t}\}$. The history vector $\mathbf{H^c_{i,t}}$ entered the model as three dummy-coded variables; no interaction terms further improved the fit.

Overall, the vector of regression coefficients for the *i*th individual, $\mathbf{Y}_{i,t-c}$, consisted of three years of asthma history, and $\mathbf{X}_i$, covariates vector including covariates of interest and the index year;

and with the first element being 1 to capture the intercept. This ordinal logistic regression model calculates three probabilities, $Pr\left(Y_{i,t+1} > k|\mathbf{X}_i, \boldsymbol{H}_{i,t}^{\mathbf{c}}\right)$, for severity threshold k=0, 1, 2:

Eq.(1): $logit\left[Pr\left(Y_{i,t+1} > k|\mathbf{X}_i, \boldsymbol{H}_{i,t}^{\mathbf{c}}\right)\right] = \boldsymbol{\beta}_k.\mathbf{X}_i + \boldsymbol{\alpha}_k^{\mathbf{c}}.\mathbf{Y}_{i,t-c}$, where c=0, 1, 2.

In Eq.(1), exponents of the $\boldsymbol{\alpha}_0$, $\boldsymbol{\alpha}_1$, $\boldsymbol{\alpha}_2$ and $\boldsymbol{\beta}_0$, $\boldsymbol{\beta}_1$, $\boldsymbol{\beta}_2$ vectors correspond to, respectively, odds ratio of the effects of covariates on entering into moderate/severe/death, into severe/death, and into death in the future year. This model by default allows regression intercepts to be different for each severity threshold $k$. Only when a variable satisfies the proportional odds assumption, the condition $\beta_0=\beta_1=\beta_2$ or $\alpha_0=\alpha_1=\alpha_2$ was enforced, thus creating a partial proportional odds model.

**Fitting the partial proportional odds model**

We followed the approach proposed by Stokes et al 2000 to fit such a model in SAS(1). As a first step, we fitted an ordinal logistic regression model with PROC LOGISTIC, which allowed us to test for proportional odds assumption for each independent variable. Then, we fitted a partial proportional odds model with PROC GENMOD, using a Generalized Linear Model (GLM) with Generalized Estimating Equation (GEE).

In specific, to fit this partial proportional odds model, we first expanded the dataset both vertically and horizontally into 3 identical datasets, then expressed the regression equation in terms of a dummy variable $P_{i,t+1}$ which, respectively for each of the 3 new datasets, represented the 3 severity thresholds of outcome variable $Y_{i,t+1}$. The translation from $Y_{i,t+1}$ to $P_{i,t+1}$ is given in Table A1. below:

| | Table A1. Translation from original dataset to the 3 augmented datasets | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Dataset** | **Severity Variable** | **Severity State** | | | | **Intercept (severity threshold)** | **Z (intercept indicator)** | **Pred** |
| Original | $Y_{i,t}$ | 0 (mild) | 1 (moderate) | 2 (severe) | 3 (death) | | | |
| New: #1 | $P_{i,t}$ | 0 | 1 | 1 | 1 | moderate/severe/death vs. mild | 0 | $P_0$ |
| New: #2 | | 0 | 0 | 1 | 1 | severe/death vs. moderate/mild | 1 | $P_1$ |
| New: #3 | | 0 | 0 | 0 | 1 | death vs. severe/moderate/mild | 2 | $P_2$ |

Obs, observations; Pred, predicted value

These 3 new datasets were combined to form one augmented dataset, the latter was used to fit a logistic model with the new severity indicator, $P_{i,t+1}$, as the dependent variable. The regression equation is given in Eq.(2) below. Given the substantial sample size of this population study and after comparison between goodness of fit associated with different working correlation structures, we assumed independent correlation between clustered data within the same individual.

**Eq.(2):**

$$logit\left[Pr\left(P_{i,t+1}\right)\right] = \beta_1.\mathrm{Y}_t + \beta_2.Z + \beta_3.(\mathrm{Y}_t \times Z) + \beta_4.\mathrm{Y}_{t-1} + \beta_5.(\mathrm{Y}_{t-1} \times Z) + \beta_6.\mathrm{Y}_{t-2} + \beta_7.(\mathrm{Y}_{t-2} \times Z) + \beta_8.Age + \beta_9.(\mathrm{Age} \times Z) + \beta_{10}.Sex + \beta_{11}.(\mathrm{Sex} \times Z) + \beta_{12}.SES + \beta_{13}.(\mathrm{SES} \times Z) + \beta_{14}.Comorbidity + \beta_{15}.(\mathrm{Comorbidity} \times Z) + \beta_{16}.PDC + \beta_{17}.(\mathrm{PDC} \times Z) + \beta_{18}.Index\ Year$$

where the interaction term between an independent variable and the intercept indicator, Z, captured the different regression intercepts for each severity threshold $k$, for variables which violated the proportional odds assumption. The indicator of index year was the only variable which met the proportional odds assumption. There was no need for index year to interact with Z because its regression intercepts would not differentiate across the 3 severity thresholds.

Appendix 5 presented regression results as odds ratios for transition between severity states, which were estimated based on the regression coefficients of the variable itself and the interaction term between the variable and Z.

Predicted values $P_0$, $P_1$ and $P_2$ from the abovementioned logistic model showed, respectively, the probability of transition to moderate/severe/death versus to mild, to severe/death versus to moderate/mild, and to death versus to severe/moderate/mild, in the future year. Based on these predictions, we were able to calculate the likelihood of future severity, i.e., $Q_i$, using the likelihood function given in Table A2:

**Table A2. Likelihood Function of Future Severity**

| $Y_{i,t+1}$(severity) | $Q_i$ (likelihood) |
|---|---|
| 0 (mild) | $1 - P_1$ |
| 1 (moderate) | $P_2 - P_1$ |
| 2 (severe) | $P_3 - P_2$ |
| 3 (death) | $P_3$ |

**Estimation of 10-year disease trajectory**

The final Markov model consistent of 28 states (mild/moderate/severe asthma within the current and past 2 years=27 states, plus a state representing death), as shown in Appendix 3. Thus, our model quantifies the trajectory of asthma severity by calculating a 28-state transition probability matrix representing the likelihood of being in a given severity state in the next year for a patient with a given characteristics and severity history in the current year and past 2 years.

For each individual, the predicted probabilities of transitioning to a particular severity state given a modified set of covariates $\mathbf{X}'_i$, representing possibly counterfactual scenarios (e.g., high SES versus low SES in the index year), were calculated for all potential asthma severity histories. Such probabilities were used to evolve the multi-state Markov model of asthma for 10 years, with initial state values being the observed asthma history in the index year and pre-index 2 years, i.e., $\mathbf{H}^{c}_{i,0}=\{Y_{i,-2}, Y_{i,-1}, Y_{i,0}\}$. To plot the population-averaged trajectories of asthma severity, marginal state probabilities associated with the (possibly counterfactual) scenarios were calculated by averaging state probabilities for each individual across the population within each year of follow-up, setting other covariates of each individual to the observed values(2).

**References of Appendix 3**

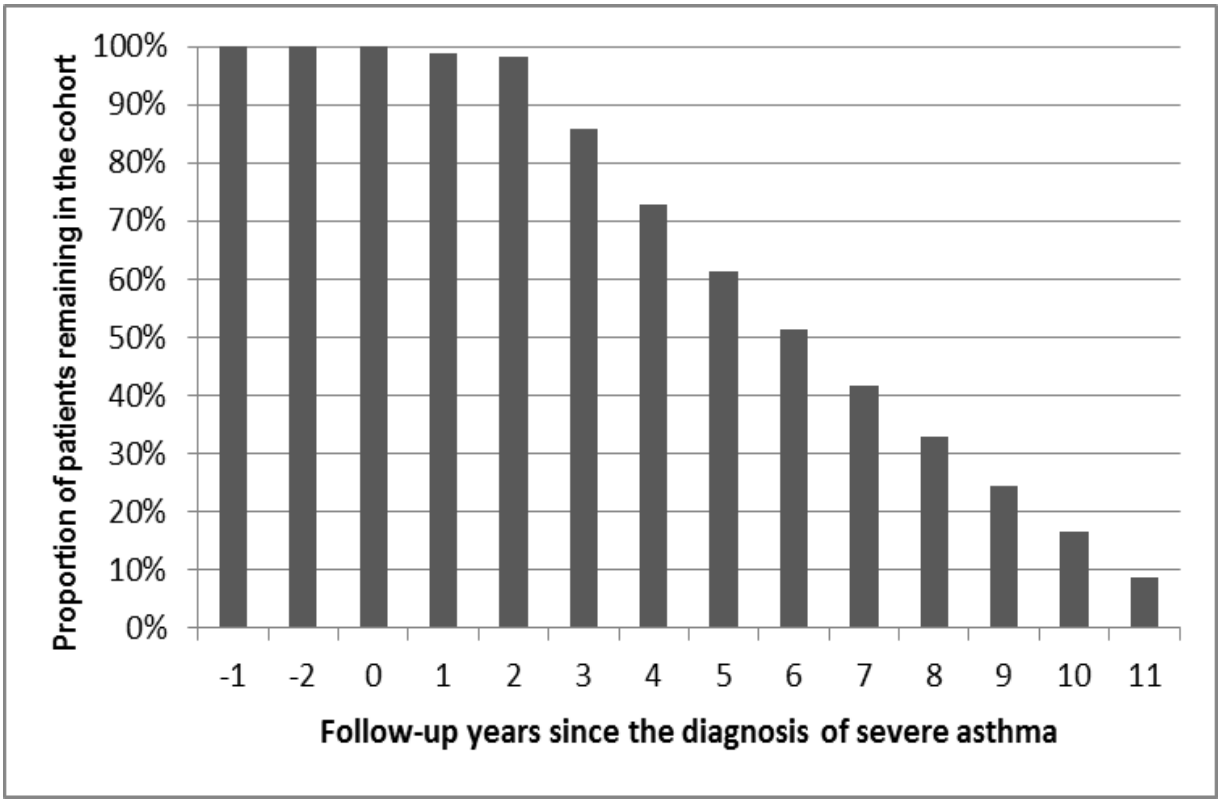
1. Stokes, M. E., Davis, C. S., and Koch, G. G. Categorical Data Analysis Using the SAS System, Second Edition, Cary, NC: SAS Institute Inc. 2000. p533-41.

2. Austin PC, Urbach DR: Using G-computation to estimate the effect of regionalization of surgical services on the absolute reduction in the occurrence of adverse patient outcomes. Med Care. 2013 Sep;51(9):797–805.

**Appendix 3. The 28-states transition probability matrix of the Markov model**

| Asthma Severity in the Past 3 years | | | Probability of Severity Level in Year (T+1) | | | |
|---|---|---|---|---|---|---|
| **Year (T-2)** | **Year (T-1)** | **Year T** | **Mild** | **Moderate** | **Severe** | **Death** |
| Mild | Mild | Mild | $\Pi_{0000}$ | $\Pi_{0001}$ | $\Pi_{0002}$ | $\Pi_{0003}$ |
| Moderate | Mild | Mild | $\Pi_{1000}$ | $\Pi_{1001}$ | $\Pi_{1002}$ | $\Pi_{1003}$ |
| Severe | Mild | Mild | $\Pi_{2000}$ | $\Pi_{2001}$ | $\Pi_{2002}$ | $\Pi_{2003}$ |
| Mild | Moderate | Mild | $\Pi_{0100}$ | $\Pi_{0101}$ | $\Pi_{0102}$ | $\Pi_{0103}$ |
| Moderate | Moderate | Mild | $\Pi_{1100}$ | $\Pi_{1101}$ | $\Pi_{1102}$ | $\Pi_{1103}$ |
| Severe | Moderate | Mild | $\Pi_{2100}$ | $\Pi_{2101}$ | $\Pi_{2102}$ | $\Pi_{2103}$ |
| Mild | Severe | Mild | $\Pi_{0200}$ | $\Pi_{0201}$ | $\Pi_{0202}$ | $\Pi_{0203}$ |
| Moderate | Severe | Mild | $\Pi_{1200}$ | $\Pi_{1201}$ | $\Pi_{1202}$ | $\Pi_{1203}$ |
| Severe | Severe | Mild | $\Pi_{2200}$ | $\Pi_{2201}$ | $\Pi_{2202}$ | $\Pi_{2203}$ |
| Mild | Mild | Moderate | $\Pi_{0010}$ | $\Pi_{0011}$ | $\Pi_{0012}$ | $\Pi_{0013}$ |
| Moderate | Mild | Moderate | $\Pi_{1010}$ | $\Pi_{1011}$ | $\Pi_{1012}$ | $\Pi_{1013}$ |
| Severe | Mild | Moderate | $\Pi_{2010}$ | $\Pi_{2011}$ | $\Pi_{2012}$ | $\Pi_{2013}$ |
| Mild | Moderate | Moderate | $\Pi_{0110}$ | $\Pi_{0111}$ | $\Pi_{0112}$ | $\Pi_{0113}$ |
| Moderate | Moderate | Moderate | $\Pi_{1110}$ | $\Pi_{01111}$ | $\Pi_{1112}$ | $\Pi_{1113}$ |
| Severe | Moderate | Moderate | $\Pi_{2110}$ | $\Pi_{21111}$ | $\Pi_{2112}$ | $\Pi_{2113}$ |
| Mild | Severe | Moderate | $\Pi_{0210}$ | $\Pi_{0211}$ | $\Pi_{0212}$ | $\Pi_{0213}$ |
| Moderate | Severe | Moderate | $\Pi_{1210}$ | $\Pi_{1211}$ | $\Pi_{1212}$ | $\Pi_{1213}$ |
| Severe | Severe | Moderate | $\Pi_{2210}$ | $\Pi_{2211}$ | $\Pi_{2212}$ | $\Pi_{2213}$ |
| Mild | Mild | Severe | $\Pi_{0020}$ | $\Pi_{0021}$ | $\Pi_{0022}$ | $\Pi_{0023}$ |
| Moderate | Mild | Severe | $\Pi_{1020}$ | $\Pi_{1021}$ | $\Pi_{1022}$ | $\Pi_{1023}$ |
| Severe | Mild | Severe | $\Pi_{2020}$ | $\Pi_{2021}$ | $\Pi_{2022}$ | $\Pi_{2023}$ |
| Mild | Moderate | Severe | $\Pi_{0120}$ | $\Pi_{0121}$ | $\Pi_{0122}$ | $\Pi_{0123}$ |
| Moderate | Moderate | Severe | $\Pi_{1120}$ | $\Pi_{1121}$ | $\Pi_{1122}$ | $\Pi_{1123}$ |
| Severe | Moderate | Severe | $\Pi_{2120}$ | $\Pi_{2121}$ | $\Pi_{2122}$ | $\Pi_{2123}$ |
| Mild | Severe | Severe | $\Pi_{0220}$ | $\Pi_{0221}$ | $\Pi_{0222}$ | $\Pi_{0223}$ |
| Moderate | Severe | Severe | $\Pi_{1220}$ | $\Pi_{1221}$ | $\Pi_{1222}$ | $\Pi_{1223}$ |
| Severe | Severe | Severe | $\Pi_{2220}$ | $\Pi_{2221}$ | $\Pi_{2222}$ | $\Pi_{2223}$ |
| Any | Any | Death | 0 | 0 | 0 | 1 |

**Appendix 4. Proportions of patients remaining in the study cohort over the follow-up period.**



**Appendix 5. Adjusted odds ratio of transition to different severity states, full results from the main regression model.**

| Co-variable | Asthma severity in the next year (year T+1) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Moderate, severe asthma & death vs mild asthma | | | | Severe asthma/death vs mild/moderate asthma | | | | Death vs. mild/moderate/severe asthma | | | |
| | OR | 95% CI | | p-value | OR | 95% CI | | p-value | OR | 95% CI | | p-value |
| Severity in year T | | | | | | | | | | | | |
| Mild | Reference | | | | Reference | | | | Reference | | | |
| Moderate | **6.86** | **6.54** | **7.20** | **<.0001** | **3.39** | **3.12** | **3.68** | **<.0001** | 0.91 | 0.67 | 1.23 | 0.538 |
| Severe | **14.95** | **13.89** | **16.08** | **<.0001** | **13.88** | **12.74** | **15.12** | **<.0001** | **1.78** | **1.30** | **2.44** | **0.000** |
| Severity in year T-1 | | | | | | | | | | | | |
| Mild | Reference | | | | Reference | | | | Reference | | | |
| Moderate | **2.55** | **2.40** | **2.70** | **<.0001** | **1.39** | **1.27** | **1.51** | **<.0001** | 1.04 | 0.73 | 1.50 | 0.814 |
| Severe | **2.79** | **2.63** | **2.97** | **<.0001** | **2.78** | **2.55** | **3.02** | **<.0001** | 1.41 | 1.00 | 1.98 | 0.050 |
| Severity in year T-2 | | | | | | | | | | | | |
| Mild | Reference | | | | Reference | | | | Reference | | | |
| Moderate | **1.81** | **1.71** | **1.91** | **<.0001** | **1.17** | **1.09** | **1.25** | **<.0001** | 0.89 | 0.66 | 1.20 | 0.457 |
| Severe | **1.75** | **1.65** | **1.85** | **<.0001** | **1.86** | **1.73** | **2.00** | **<.0001** | 1.00 | 0.74 | 1.35 | 0.996 |
| Baseline age | **1.01** | **1.01** | **1.01** | **<.0001** | **1.01** | **1.01** | **1.01** | **<.0001** | **1.05** | **1.04** | **1.06** | **<.0001** |
| Sex | | | | | | | | | | | | |
| Female | Reference | | | | Reference | | | | Reference | | | |
| Male | **1.12** | **1.07** | **1.16** | **<.0001** | 1.01 | 0.96 | 1.05 | 0.812 | **1.73** | **1.41** | **2.12** | **<.0001** |
| Baseline SES | | | | | | | | | | | | |
| Low | Reference | | | | Reference | | | | Reference | | | |
| Middle | 0.98 | 0.93 | 1.04 | 0.508 | 0.94 | 0.89 | 1.00 | 0.059 | **0.59** | **0.44** | **0.79** | **0.000** |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| High | 0.98 | 0.94 | 1.03 | 0.445 | **0.88** | **0.84** | **0.93** | **<.0001** | **0.56** | **0.44** | **0.72** | **<.0001** |
| Baseline Comorbidity | | | | | | | | | | | | |
| CCI score=0 | Reference | | | | Reference | | | | Reference | | | |
| CCI score=1 | 1.05 | 0.99 | 1.12 | 0.101 | **1.08** | **1.01** | **1.16** | **0.020** | **0.72** | **0.54** | **0.96** | **0.025** |
| CCI score=2 | 1.11 | 0.99 | 1.24 | 0.080 | **1.32** | **1.17** | **1.49** | **<.0001** | **1.94** | **1.32** | **2.87** | **0.001** |
| CCI score=3 | 1.05 | 0.92 | 1.19 | 0.466 | **1.48** | **1.29** | **1.70** | **<.0001** | **4.24** | **2.96** | **6.09** | **<.0001** |
| Baseline PDC | | | | | | | | | | | | |
| PDC<0.5 | Reference | | | | Reference | | | | Reference | | | |
| 0.5<=PDC<0.8 | **1.07** | **1.02** | **1.12** | **0.008** | **1.22** | **1.16** | **1.29** | **<.0001** | 1.10 | 0.88 | 1.39 | 0.400 |
| PDC>=0.8 | **1.20** | **1.11** | **1.30** | **<.0001** | **1.26** | **1.17** | **1.35** | **<.0001** | 0.87 | 0.62 | 1.22 | 0.414 |
| Baseline calendar yeare | 1.00 | 0.99 | 1.00 | 0.210 | 1.00 | 0.99 | 1.00 | 0.210 | 1.00 | 0.99 | 1.00 | 0.210 |

Abbreviations: CI, confidence interval; OR, odds ratio; PDC, proportion of days covered

Bold texts indicate statistical significance with a p-value of less than 0.05.

**Appendix 6. Regression results for including severity history in the past 4 years, controlling for covariates in the main regression model.**

| History variable | Asthma severity in the next year (year T+1) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Moderate, severe asthma & death vs mild asthma | | | | Severe asthma/death vs mild/moderate asthma | | | | Death vs. mild/moderate/severe asthma | | | |
| | OR | 95% CI | | p-value | OR | 95% CI | | p-value | OR | 95% CI | | p-value |
| Severity in year T | | | | | | | | | | | | |
| Mild | Reference | | | | Reference | | | | Reference | | | |
| Moderate | **6.60** | **6.28** | **6.93** | **<.0001** | **3.34** | **3.07** | **3.63** | **<.0001** | 0.88 | 0.64 | 1.21 | 0.44 |
| Severe | **14.02** | **13.00** | **15.13** | **<.0001** | **13.23** | **12.11** | **14.45** | **<.0001** | **1.71** | **1.22** | **2.38** | **0.002** |
| Severity in year T-1 | | | | | | | | | | | | |
| Mild | Reference | | | | Reference | | | | Reference | | | |
| Moderate | **2.41** | **2.28** | **2.56** | **<.0001** | **1.36** | **1.24** | **1.48** | **<.0001** | 1.06 | 0.73 | 1.53 | 0.759 |
| Severe | **2.85** | **2.68** | **3.03** | **<.0001** | **2.79** | **2.56** | **3.04** | **<.0001** | 1.40 | 0.98 | 2.00 | 0.066 |
| Severity in year T-2 | | | | | | | | | | | | |
| Mild | Reference | | | | Reference | | | | Reference | | | |
| Moderate | **1.59** | **1.50** | **1.69** | **<.0001** | **1.10** | **1.02** | **1.19** | **0.010** | 0.86 | 0.62 | 1.19 | 0.364 |
| Severe | **1.59** | **1.49** | **1.69** | **<.0001** | **1.72** | **1.59** | **1.86** | **<.0001** | 0.94 | 0.68 | 1.31 | 0.724 |
| Severity in year T-3 | | | | | | | | | | | | |
| Mild | Reference | | | | Reference | | | | Reference | | | |
| Moderate | **1.52** | **1.44** | **1.61** | **<.0001** | 1.07 | 1.00 | 1.14 | 0.051 | 1.09 | 0.82 | 1.44 | 0.557 |
| Severe | **1.50** | **1.41** | **1.59** | **<.0001** | **1.53** | **1.43** | **1.64** | **<.0001** | 1.03 | 0.76 | 1.38 | 0.868 |

Abbreviations: CI, confidence interval; OR, odds ratio; PDC, proportion of days covered

Bold texts indicate statistical significance with a p-value of less than 0.05.