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Medication use in uncontrolled pediatric asthma: Results from the SysPharmPediA study

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ABSTRACT

Background: Uncontrolled pediatric asthma has a large impact on patients and their caregivers. More insight into determinants of uncontrolled asthma is needed. We aim to compare treatment regimens, inhaler techniques, medication adherence and other characteristics of children with controlled and uncontrolled asthma in the: Systems Pharmacology approach to uncontrolled Paediatric Asthma (SysPharmPediA) study.
Material and methods: 145 children with moderate to severe doctor-diagnosed asthma (91 uncontrolled and 54 controlled) aged 6–17 years were enrolled in this multicountry, (Germany, Slovenia, Spain, and the Netherlands) observational, case-control study. The definition of uncontrolled asthma was based on asthma symptoms and/or exacerbations in the past year. Patient-reported adherence and clinician-reported medication use were assessed,

Abbreviations: SysPharmPediA, systems pharmacology approach to uncontrolled paediatric asthma; GINA, global initiative of asthma; ICS, Inhaled corticosteroids; LTRA, leukotriene receptor antagonists; LABA, long-acting Beta2-agonists; OCS, oral corticosteroids; SABA, short-acting Beta2-agonists; MARS, medication adherence rating scale; FEV_1, forced expiratory volume in one second; Δ FEV_1% predicted, difference between FEV_1% predicted post and pre salbutamol; ACQ, asthma control questionnaire; ACT, asthma control test; SPC, summary of product characteristics; MDI, metered dose inhaler; DPI, dry powder inhaler; AIC, akaike information criterion.

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as well as lung function and inhalation technique. A logistic regression model was fitted to assess determinants of uncontrolled pediatric asthma.
Results: Children in higher asthma treatment steps had a higher risk of uncontrolled asthma (OR (95%CI): 3.30 (1.56–7.19)). The risk of uncontrolled asthma was associated with a larger change in FEV_1% predicted post and pre-salbutamol (OR (95%CI): 1.08 (1.02–1.15)). Adherence and inhaler techniques were not associated with risk of uncontrolled asthma in this population.
Conclusion: This study showed that children with uncontrolled moderate-to-severe asthma were treated in higher treatment steps compared to their controlled peers, but still showed a higher reversibility response to salbutamol. Self-reported adherence and inhaler technique scores did not differ between controlled and uncontrolled asthmatic children. Other determinants, such as environmental factors and differences in biological profiles, may influence the risk of uncontrolled asthma in this moderate to severe asthmatic population.

1. Introduction

Asthma is the most common chronic disease among European children (von Mutius, 2000). Although asthma can be controlled with medication in most children, a small group (approximately 2%) suffers from severe asthma despite treatment (Nordlund et al., 2014). Asthma can be a significant public health problem when it is not under control despite prescribed medication. It may require the use of emergency care, might lead to hospital admissions, and increases the number of missed school days of the child and working days of the parents (Masoli et al., 2004).

The main aims of asthma management in children are to achieve asthma control, limit future asthma exacerbations and prevent lung function decline (GINA, 2016). Asthma control is defined as the degree to which asthma manifestations are reduced or prevented by therapy (Dinakar and Chipps, 2017). Identifying factors that may influence asthma control in children in order to personalize their treatment is challenging for pediatricians and researchers. These factors include among others: differences in asthma phenotype, poor adherence to asthma medications, inadequate inhaler techniques, psychological factors, socioeconomic factors, comorbidities, and continuous environmental exposure to allergens, cigarette smoke, or air pollution (Yawn, 2008).

Asthma therapy mainly consists of maintenance treatment with inhaled corticosteroids (ICS) with or without long-acting beta2-agonist (LABA) combined with short-acting beta2-agonists (SABA) as reliever treatment (Reddel et al., 2021). Both therapies have shown to be effective in controlling asthma symptoms, improving lung function, and reducing exacerbations (O'Byrne et al., 2005). In most practice guidelines, leukotriene receptor antagonists (LTRA) are considered as add-on therapy to ICS and LABA in children with persistent asthma (Doherty, 2007).

In the past years, the introduction of biologics (monoclonal antibodies) has expanded treatment options for severe therapy-resistant asthma (Slob et al., 2019). However, biologics are expensive, and treatment is intensive with frequent subcutaneous injections (mostly every 2–8 weeks for children) (Licari et al., 2018). Indeed injections are potentially burdensome for children. In addition, there is a paucity of evidence on the efficacy of biologics in severe childhood asthma (Brusselle and Koppelman, 2022).

The Systems Pharmacology approach to uncontrolled Paediatric Asthma (SysPharmPediA) consortium investigates differences between children treated with inhaled corticosteroids with uncontrolled and controlled asthma using a systems medicine approach. Although -omics profiles (such as microbiomics, (*epi*)genomics, transcriptomics, and metabolomics) may differ between uncontrolled and controlled asthma in children (Farzan et al., 2018), the first step is to assess the possible differences in medication adherence and inhaler technique, to explore whether this could explain poor asthma control. The present study aims to compare medication use, medication adherence, inhaler technique, inhaler device types, and other factors that might influence asthma control (lung function, smoking exposure, ethnicity, age, sex, season of inclusion, and country of inclusion) between controlled and uncontrolled moderate-to-severe pediatric asthma patients included in the SysPharmPediA study.

2. Material and methods

2.1. Study population

The study population and design have previously been described in detail (Clinicaltrials.gov identifier: NCT04865575) (Abdel-Aziz et al., 2021). Briefly, the inclusion criteria were: (1) children age range 6 to 17 years; (2) doctor-diagnosed asthma; (3) moderate to severe asthma under GINA (Global INitiative of Asthma) (GINA, 2016) treatment Step 2 or higher. Participants with uncontrolled or controlled asthma were included after screening at the outpatient clinic or during hospitalization due to an exacerbation in tertiary centers in four European countries (the Netherlands, Germany, Spain, and Slovenia). Uncontrolled children with asthma recruited at the outpatient clinic were on Global INitiative of Asthma (GINA) (GINA, 2016) step 3 or higher and one or more of the following criteria: (1) $\geq$1 exacerbation(s) in the past year requiring oral corticosteroids (OCS) use and/or, (2) in the previous year, $\geq$1 exacerbation(s) that necessitated hospitalization or ER visits. and/or, (3) Asthma Control Test (ACT) $\leq$ 19 (Liu et al., 2007; Nathan et al., 2004). In addition, uncontrolled children with asthma were included during hospitalization due to an exacerbation and had to be on asthma treatment GINA step 2 or higher. Patients with controlled asthma met the following inclusion criteria: (1) no exacerbations that required the use of OCS, hospitalizations, or visiting the emergency room in the previous year, and (2) ACT scores ($>$ 19) indicating that asthma is currently controlled. This study was carried out in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the University Medical Center Utrecht, Utrecht, the Netherlands (NL55788.041.15); the ethics committee of University Regensburg, Germany (18–1034–101); Clinical Research Ethics Committee of the Basque Country, Spain (PI2015075 (SO)); National Medical Ethics Committee, Slovenia (0120–569/2017/4)). In addition, all participants in the study gave their informed consent.

2.2. Data collection

All study participants visited the outpatient clinic of one of the tertiary hospitals to undergo the following study procedures: clinical evaluation, spirometry with bronchodilator reversibility, asthma questionnaires, and assessment of medication use (Abdel-Aziz et al., 2021). Additional clinical data were gathered from hospital patient files, physician reports, and questionnaires completed by patients or their parents. The collected data were integrated into a standardized monitored online database (www.Qnome.eu). QNOME is provided by MaganaMed GmbH, Regensburg, Germany (Brandstetter et al., 2019). Before any analyses were conducted, the data underwent quality checking and data cleaning steps.

2.3. Outcomes

Medication use was evaluated (1) per medication category (ICS, LABA, LTRA, biologics, and OCS) and (2) per GINA treatment step (GINA, 2016). Following the GINA guideline 2016 (this version was the current version of the guideline when children were included), all participants were categorized in steps 3, 4, and 5 based on their medication profiles. The self-reported 9-item Medication Adherence Rating Scale (MARS) was used to determine medication adherence (Mora et al., 2011). Responses were given by the parents and/or children on a 5-point Likert scale (always, often, sometimes, rarely, never) and indicated how often the non-adherent behavior occurred. The total MARS score can vary from 9 (no adherence) to 45 (high adherence). Item 2 of the MARS scale can be used to identify unintentional non-adherence. In contrast, items 1, 3, 5, and 6 were used to identify intentional non-adherence. Unintentional non-adherence was considered a score of 1–5 on item 2, and intentional non-adherence as a total score of 4–20 on questions 1, 3, 5, and 6.

Inhalation technique was scored during the study visit, utilizing device-specific questionnaires (van der Palen et al., 1999) by a trained research nurse or pediatrician. According to the summary of product characteristics (SPC), the inhaler technique score was calculated as a percentage completed of all the required steps for a proper inhaler according to the summary of product characteristics (SPC). Spirometry before and after 400 μg salbutamol inhalation was undertaken in all subjects to define bronchodilator reversibility. The Global Lung Function Initiative (GLI) equations (Quanjer et al., 2012) were used to compute the percentage predicted of lung function measures, as recommended by the European Respiratory Society/American Thoracic Society (ERS/ATS) (Miller et al., 2005). Subjects were grouped based on ethnicity into Caucasian and non-Caucasian. The definition of ethnicity has previously been described in detail (Abdel-Aziz et al., 2021). Current active/passive smokers were defined as those who were smokers or had a smoker in their family at the time of inclusion based on the self-reported questionnaire completed by patients or parents.

2.4. Statistical analysis

The Kolmogorov-Smirnov test and visualization techniques (histograms and Q-Q plots) were used to determine the distribution of continuous variables. Continuous data with a normal distribution were presented as mean ± SD and the median and 25th – 75th percentiles were used to describe non-normally distributed continuous data. Possible differences in age, sex, ethnicity, the season of inclusion, country of inclusion, GINA steps, asthma medication intake in the past year (such as daily dose of ICS), ICS inhaler device types, LABA inhaler device types, FEV_1% predicted pre-salbutamol, FEV_1% predicted post-salbutamol, change in FEV_1% predicted values post and pre salbutamol (Δ FEV_1% predicted), reversibility criteria (defined as an increase in FEV_1 of ≥ 12% from baseline after salbutamol inhalation (GINA, 2016), current active/passive smoking, inhaler technique score, and adherence (defined as MARS score) were evaluated by Mann-Whitney U test, Pearson Chi-Square tests, or Fisher's Exact test as appropriate. Only one participant in the controlled group received GINA treatment step 5, so a logistic regression model could not be applied to this treatment group. Hence, we combined GINA treatment steps 4 and 5 to create a new subgroup called GINA treatment steps 4/5 in order to assess the association between GINA treatment steps and the risk of uncontrolled asthma. We first examined unadjusted associations between all potentially relevant independent variables (variables with a p-value <0.10 in Table 1 or based on previous studies and discussions with experts in the field) and the odds of uncontrolled asthma by logistic regression. We then used a backward selection approach to identify the final important predictors of uncontrolled asthma in children included in this study. We started with a model that contained all candidate variables: age (continuous), sex (male and female), ethnicity (Caucasian;

Table 1
Baseline characteristics of participants included in SysPharmPediA.

Characteristics	Total (n = 145)	Uncontrolled asthma (n = 91)	Controlled asthma (n = 54)	P-value Uncontrolled vs controlled
Age, years, median (25th – 75th percentiles)	11.93 (9.65 - 14.00)	12.00 (9.68 - 14.00)	11.74 (9.65 - 13.84)	0.699
Sex, n (%)				0.490
Male	86/145 (59%)	52/91 (57%)	34/54 (63%)	
Ethnicity, n (%)				**< 0.001**
Caucasian	111/144 (77%)	61/90 (68%)	50/54 (93%)	
Season of inclusion, n (%)				0.496
■ **Spring**	41/145 (28%)	26/91 (29%)	15/54 (28%)	
■ **Summer**	46/145 (32%)	28/91 (31%)	18/54 (33%)	
■ **Autumn**	31/145 (21%)	17/91 (19%)	14/54 (26%)	
■ **Winter**	27/145 (19%)	20/91 (22%)	7/54 (13%)	
Country of inclusion, n (%)				**0.014**
■ **Spain**	50/145 (34%)	35/91 (38%)	15/54 (28%)	
■ **Germany**	39/145 (27%)	20/91 (22%)	19/54 (35%)	
■ **The Netherlands**	33/145 (23%)	26/91 (29%)	7/54 (13%)	
■ **Slovenia**	23/145 (16%)	10/91 (11%)	13/54 (24%)	
GINA steps *, n (%)				**< 0.001**
■ **Step 3**	65/145 (45%)	28/91 (31%)	37/54 (69%)	
■ **Step 4**	64/145 (44%)	48/91 (53%)	16/54 (30%)	
■ **Step 5**	16/145 (11%)	15/91 (16%)	1/54 (2%)	
Current asthma medication intake, n (%)				
LABA	136/145 (94%)	84/91 (92%)	52/54 (96%)	0.487
ICS	145/145 (100%)	91/91 (100%)	54/54 (100%)	–
OCS (maintenance)	4/145 (3%)	4/91 (4%)	0/54 (0%)	0.297
LTRA	25/145 (17%)	18/91 (20%)	7/54 (13%)	0.293
Omalizumab	15/145 (10%)	14/91 (15%)	1/54 (2%)	**0.01**
Mepolizumab	2/145 (1%)	2/91 (2%)	0/54 (0%)	0.523
Low, medium and high daily doses of ICS **, n (%)				**< 0.001**
■ **Low**	66/145 (46%)	29/91 (32%)	37/54 (69%)	
■ **Medium**	46/145 (32%)	31/91 (34%)	15/54 (28%)	
■ **High**	33/145 (23%)	31/91 (34%)	2/54 (4%)	
ICS inhaler type, n (%)				0.915
■ **MDI**	79/145 (54%)	50/91 (55%)	29/54 (54%)	
■ **DPI**	65/145 (45%)	40/91 (44%)	25/54 (46%)	
■ **Both MDI & DPI**	1/145 (1%)	1/91 (1%)	0/54 (0%)	
LABA inhaler type, n (%)				0.661
■ **MDI**	71/145 (49%)	44/91 (48%)	27/54 (50%)	
■ **DPI**	63/145 (43%)	38/91 (42%)	25/54 (46%)	
■ **Both MDI & DPI**	2/145 (1%)	2/91 (2%)	0/54 (0%)	
■ **Non LABA user**		7/91 (8%)	2/54 (4%)	

(continued on next page)

Table 1 (*continued*)

Characteristics	Total ($n = 145$)	Uncontrolled asthma ($n = 91$)	Controlled asthma ($n = 54$)	P-value Uncontrolled vs controlled
	9/145 (6%)			
FEV_1% predicted pre-salbutamol, median (25th – 75th percentiles)	94.14 (82.74 - 103.25) ($n = 142$)	95.40 (82.05 - 103.22) ($n = 89$)	92.64 (86.08 - 103.26) ($n = 53$)	0.833
FEV_1% predicted post-salbutamol, median (25th – 75th percentiles)	99.55 (89.97 - 108.76) ($n = 140$)	99.98 (92.13 - 108.01) ($n = 88$)	97.63 (89.44 - 109.35) ($n = 52$)	0.366
Δ FEV_1% predicted, median (25th – 75th percentiles)	4.29 (0.59 - 9.89) ($n = 140$)	6.44 (1.57 - 11.69) ($n = 88$)	2.84 (0.43 - 7.38) ($n = 52$)	**0.013**
Bronchodilator reversability *, n (%)**	33/140 (24%)	25/88 (28%)	8/52 (15%)	0.079
ACT score, median (25th – 75th percentiles)	23.00 (19.00 – 25.00) ($n = 140$)	20.00 (17.00 – 23.00) ($n = 88$)	24.50 (23.00 – 25.00) ($n = 52$)	**< 0.001**
Current active/ passive smoking, n (%)	42/138 (30%)	26/87 (30%)	16/51 (31%)	0.855
Inhaler technique score, median (25th – 75th percentiles)	100.00 (90.91 - 100) ($n = 97$)	100.00 (90.91 - 100) ($n = 60$)	100.00 (90.91 - 100) ($n = 37$)	0.293
MARS score-total, median (25th – 75th percentiles)	43.00 (40.50 - 44.00) ($n = 127$)	43.00 (40.00 - 44.50) ($n = 79$)	44.00 (42.00 - 44.00) ($n = 48$)	0.428
MARS Q2-unintentional, median (25th – 75th percentiles)	4.00 (4.00 - 5.00) ($n = 138$)	4.00 (4.00 - 5.00) ($n = 85$)	4.00 (4.00 - 5.00) ($n = 53$)	0.306
MARS Q1, Q3, Q5, Q6-intentional, median (25th – 75th percentiles)	20.00 (19.00 - 20.00) ($n = 130$)	20.00 (19.00 - 20.00) ($n = 81$)	20.00 (19.00 - 20.00) ($n = 49$)	0.19

GINA: Global INitiative of Asthma; ICS: Inhaled CorticoSteroids; LTRA: Leukotriene Receptor Antagonists; LABA: Long-Acting Beta2-Agonists; OCS: Oral CorticoSteroids; MARS: Medication Adherence Rating Scale; FEV_1: Forced Expiratory Volume in One second; Δ FEV_1% predicted: Difference between FEV_1% predicted post and pre salbutamol; MDI: Metered Dose Inhaler; DPI: Dry Powder Inhaler; ACT: Asthma Control Test.

* Based on GINA guideline 2016.

** Based on GINA guideline 2016, Box 8, page 15.

*** according to GINA guidelines defined as an increase in FEV_1 of ≥ 12% from baseline after salbutamol inhalation.

non-Caucasian), season of inclusion (spring, summer, autumn, and winter), country of inclusion (Germany, Slovenia, Spain, and the Netherlands), GINA treatment step (steps 3 and 4/5), current smoking exposure (yes, no), forced expiratory volume in one second (FEV_1) percentage predicted before/after salbutamol (Δ FEV_1% predicted)). The variable whose removal worsened the prediction of uncontrolled asthma to the least extent was then removed from the model. This procedure was repeated until no further variables could be deleted without a statistically significant loss of the model fit, based on the Akaike Information Criterion (AIC). All analyses were conducted using R software 4.1.1 (2021–08–10) and R Studio 2021.09.0 + 351.

3. Results

3.1. Baseline characteristics

The characteristics of the 145 children included in the SysPharm-PediA study (91 participants in the uncontrolled group and 54 in the controlled group) are presented in Table 1. The median age for both groups was 12 years (25th – 75th percentiles = 10 - 14). The majority of the study population were males, 57% and 63% of the uncontrolled and controlled asthma patients, respectively. The two groups did not differ significantly in terms of age, sex, and season of inclusion. The controlled group had 93% Caucasian participants, while the uncontrolled group had only 68% Caucasian participants. Fifty subjects from Spain, 23 from Slovenia, 39 from Germany, and 33 from the Netherlands were included in this study. Both FEV_1% predicted pre and post-salbutamol were compared between two groups (p-value for both pre and post-salbutamol > 0.05). Uncontrolled asthmatics showed higher median change in FEV_1% predicted values post and pre salbutamol (Δ FEV_1% predicted) (median = 6.44, (25th – 75th percentiles = 1.57 - 11.69)) as compared with controlled asthmatic children (median = 2.84, (25th – 75th percentiles = 0.43 - 7.38)). In total, 28% of the uncontrolled asthma patients showed bronchodilator reversibility (defined as an increase in FEV_1 of ≥ 12% from baseline after salbutamol inhalation (GINA, 2016)) compared to 15% of the controlled asthma patients (p-value = 0.079).

There were no differences observed in medication adherence (total, intentional and unintentional) between children with controlled and uncontrolled asthma (Table 1). Children with uncontrolled asthma had a median total MARS score of 43.0 (25th – 75th percentiles = 40.0 – 44.5) and for the uncontrolled group was 44.0 (25th – 75th percentiles = 42.0 – 44.0). There were no differences observed in inhaler technique scores between cases and controls; both had a median total inhaler technique score of 100% (25th – 75th percentiles = 91% - 100%).

3.2. Medication use

All included subjects were treated according to GINA step 3 or higher. More than half of the uncontrolled children were on GINA step 4 (53%), and the controlled children were mostly treated on GINA step 3 (69%).

Medication use in the two groups and the total population are presented in Table 1. While percentages of LABA use were comparable in children with uncontrolled and controlled asthma (92% versus 96%, respectively), LTRA use differed and was more commonly used by uncontrolled asthma patients (20% versus 13%, respectively). Four percent of the uncontrolled asthmatics used OCS as maintenance therapy during the last 12 months, and none of the controlled group used it. The use of biologics was higher in uncontrolled asthma: 15% of the children with uncontrolled asthma received omalizumab versus 2% of children with controlled asthma, and 2% of the children with uncontrolled asthma were on mepolizumab versus none of the controlled. The results of medication use in the past 12 months did not show a difference between the two groups regarding the use of LABA, OCS, LTRA, and mepolizumab. There was a difference between the two groups regarding the use of omalizumab (15% in the uncontrolled group versus 2% in the controlled group). Also, there was a difference between the two groups in the daily dose of ICS use based on GINA guideline classification 2016 (GINA, 2016); low-medium-high dose classification (In the uncontrolled group, 32%, 34%, and 34% for low, medium, and high, respectively, compared to 69%, 28%, and 4% in the controlled group for low, medium, and high, respectively.). There was no difference between uncontrolled and controlled groups regarding ICS inhaler device types and LABA inhaler device types (Table 1).

3.3. Logistic regression

Unadjusted associations between candidate variables and the risk of uncontrolled asthma are shown in Table 2. Non-Caucasians showed a higher odds of uncontrolled asthma compared to Caucasians (unadjusted odds ratio (OR) (95% CI): 5.94 (2.16 - 21.03)). We also observed an association between GINA treatment step and the risk of uncontrolled asthma. The unadjusted odds ratio of GINA treatment step 4/5 compared to GINA treatment step 3 was 4.90 (95% CI: 2.40 - 10.33). Furthermore, there was an association between change in FEV_1% predicted values post and pre-salbutamol (Δ FEV_1% predicted) and the odds of uncontrolled asthma (unadjusted OR (95% CI): 1.08 (1.02 - 1.14) (Table 2).

The final model predicting the odds of uncontrolled asthma included GINA treatment step and bronchodilator response:

$$\ln(\text{odds})_{\text{uncontrolledasthma}} = -0.45 + 1.23\,\text{I}(X_1 = 1) + 0.07X_2$$

X_1: 0, 1 for GINA treatment step 3, and steps 4/5, respectively.
X_2: Difference between FEV_1 percentage predicted post and pre-salbutamol.

Children at treatment step 4/5 had a higher odds of uncontrolled asthma than children at treatment step 3 (OR 3.30 (95% CI: 1.56 – 7.19)). In addition, there was a higher odds of uncontrolled asthma for individuals with more bronchodilator reversibility (OR (95% CI) per one unit change: 1.08 (1.02 – 1.15)) (Table 3 and Fig. 1).

4. Discussion

In the SysPharmPediA study, we did not find differences in medication adherence and inhaler technique between children with uncontrolled and controlled asthma. There was no statistical difference in FEV_1 between the two groups before and after salbutamol administration. However, the uncontrolled asthma group showed more bronchodilator reversibility.

Furthermore, our study showed a difference in medication levels between children with controlled and uncontrolled asthma. Children with uncontrolled moderate-to-severe asthma were treated in higher treatment steps compared to their controlled peers, but still showed a higher reversibility response to salbutamol. Despite that, these patients were uncontrolled, suggesting that other factors might play a role, e.g., environmental factors or differences in underlying pathophysiological mechanisms.

Table 2
Unadjusted associations between candidate variables and the risk of uncontrolled asthma.

Variable	n	Group	OR (95% CI)
Age	145	–	0.97* (0.86 - 1.09)
Sex	145	Female	Ref
		Male	0.78 (0.39 - 1.56)
Ethnicity	144	Caucasian	Ref
		Non-Caucasian	5.94 (2.16 - 21.03)
Season of inclusion	145	Spring	Ref
		Summer	0.90 (0.37 - 2.14)
		Autum	0.70 (0.27 - 1.82)
		Winter	1.65 (0.58 - 5.02)
Country of inclusion	145	Germany	Ref
		The Netherlands	3.53 (1.28 - 10.58)
		Slovenia	0.73 (0.25 - 2.05)
		Spain	2.22 (0.93 - 5.38)
GINA step**	145	Step 3	Ref
		Step 4/5	4.90 (2.40 - 10.33)
Current active/passive smoking	138	No	Ref
		Yes	0.93 (0.44 - 2.00)
Δ FEV_1% predicted	140	–	1.08* (1.02 - 1.14)

FEV_1: Forced Expiratory Volume in One second; Δ FEV_1% predicted: Difference between FEV_1% predicted post and pre salbutamol. * per one unit increase in the variable. ** Based on GINA guideline 2016.

Table 3
Final model of backward multiple logistic regression predicting the odds of uncontrolled asthma in 134 children in the SysPharmPediA study.

Variable	OR (95% CI)
GINA Step 4/5*	3.30 (1.56 - 7.19)
Δ FEV_1% predicted	1.08 (1.02 - 1.15)

The model with the lowest Akaike information criterion (AIC) using a backward selection approach. McFadden Pseudo R squared 0.112, overall p-value <0.001, and AIC was 162.3.
* Children at GINA treatment step 3 were defined as the reference group.

The patients in this study were all from academic tertiary care hospitals where adherence to treatment is emphasized as part of standard care. However, this is not the case in the general asthma population, where adherence often influences asthmatic control (Zaeh et al., 2022). Hence, both controlled and uncontrolled asthmatic children in this study reported good medication adherence. Considering the unusually high self-reported adherence rate, self-reported adherence was not likely to be the reason for uncontrolled asthma symptoms in our study population. In addition, all of the medications studied were covered by insurance in all four countries, and all of the participants had proper insurance. Therefore, the cost of these prescriptions had no impact on medication adherence.

Our study population also showed no difference in inhaler technique between uncontrolled and controlled asthma groups. This can be related to the patient selection criteria and the willingness of the patient to participate in the SysPharmPediA study. Moreover, these children were already followed by pediatric pulmonologists, regularly checking their inhalation technique at each clinical visit. In contrast to our study, previous studies showed that the type of inhaler device could influence inhalation technique and adherence (Almomani et al., 2021). In our study, the variety of ICS and LABA inhaler devices did not influence asthma control. In addition, ethnicity has been reported to influence medication responsiveness, asthma control, and asthma severity (Gold et al., 2013; Hughes et al., 2017; Koo et al., 2016; Tay et al., 2019). In our study, there was a significant difference in ethnicity (being Caucasian or not) between the two groups (unadjusted OR (95% CI) of uncontrolled asthma: 5.94 (2.16 - 21.03)). However, ethnicity was not included in the final model. Others have found ethnic background to be associated; a study in the USA found that black children with severe or difficult-to-treat asthma had worse asthma outcomes compared to white children even upon correction for socioeconomic factors and medication use (Guilbert et al., 2019). Possibly, this may relate to differences in the genetic make-up (Kersten and Koppelman, 2021).

Children with uncontrolled asthma may have different asthma phenotypes than controlled children, resulting in an increased risk of exacerbations, despite the current asthma treatment (Wenzel, 2012). Therefore, within the SysPharmPediA study, we will assess different types of –omics to investigate whether they are linked to different asthma phenotypes.

The current study has a number of strengths. Despite the low prevalence of uncontrolled moderate-to-severe asthma in children (approximately 2% Nordlund et al., 2014), we enrolled an adequate number of these patients from four European countries. The multicentre nature of this study yields more generalizable results than single-country studies.

A potential limitation of our study is the possibility of selection bias in population and outcome measures. It is assumed that children and parents willing to participate in research are more concerned about asthma and its management (Storms, 2003) and therefore may have higher adherence and a better inhalation technique. Another limitation is the fact that more than three-quarters of our participants were

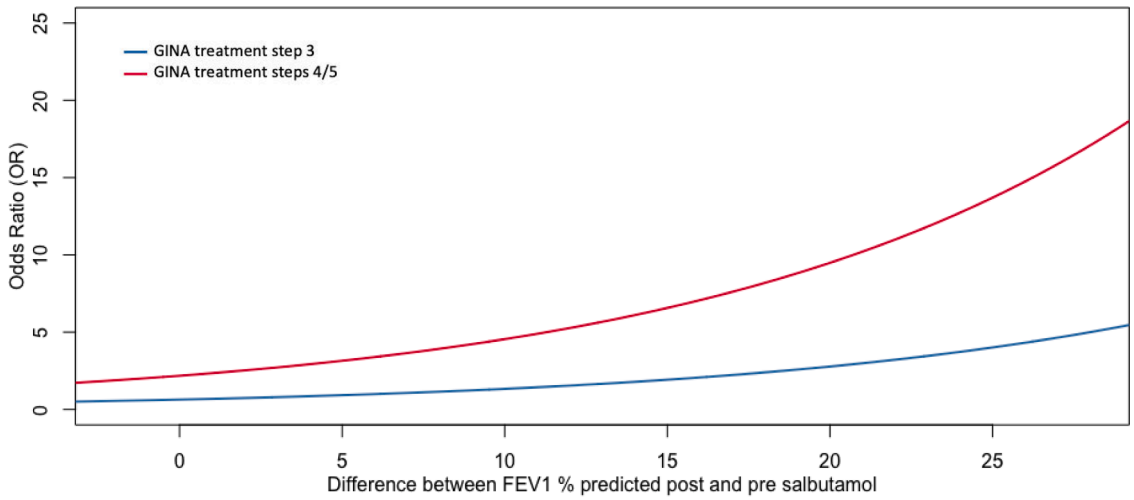

Fig. 1. Odds Ratio (OR) for uncontrolled asthma in children based on the GINA treatment step versus the difference of FEV_1 percentage predicted post and pre-salbutamol.

Caucasian. Our results may therefore not be generalizable to asthmatic children from other ethnic groups. Lastly, we evaluated medication adherence using a self-reported questionnaire. Although the MARS questionnaire is a validated measurement instrument (Mora et al., 2011), we cannot exclude the possibility that the patients' answers were influenced by social desirability. Currently, other, more objective measurement tools (such as electronic monitoring devices) are available to assess medication adherence, however, they are not always compatible with all inhalation devices.

5. Conclusions

Our results show that children with more severe asthma (defined as higher treatment steps needed to control or prevent asthma from becoming uncontrolled) had a higher risk of uncontrolled asthma. In addition, self-reported adherence to medication and inhaler technique scores did not explain differences in asthma control. A higher GINA treatment step and a greater difference in FEV_1% predicted after and before salbutamol were independently associated with the odds of uncontrolled asthma. Other determinants, such as environmental factors and differences in biological profiles, may influence the risk of uncontrolled asthma in this moderate to severe asthmatic population.

Data availability

For clinical and other data generated within the SysPharmPediA study, the authors will make them available upon specific requests subject to the requestor obtaining ethical, research, data access, and collaboration approvals from the SysPharmPediA study management board. Requests can be sent to a.h.maitland@amsterdamumc.nl.

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Declaration of Competing Interest

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Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2022.106360.

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