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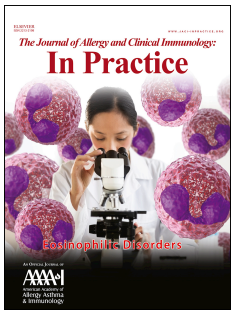

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Treatment decisions in children with asthma in a real-life clinical setting: the Swiss Paediatric Airway Cohort (SPAC)

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ABSTRACT (250 words)

Background: Asthma treatment should be modified according to symptom control and future risk, but there is scarce data on what drives treatment adjustments in routine tertiary care.

Objective: We studied factors that drive asthma treatment adjustment in paediatric outpatient clinics.

Methods: We did a cross-sectional analysis of the Swiss Paediatric Airway Cohort (SPAC), a clinical cohort of 0–16-year-old children seen by paediatric pulmonologists. We collected information on diagnosis, treatment, lung function and Fractional exhaled Nitric Oxide (FeNO) from hospital records; and on symptoms, sociodemographic and environmental factors from a parental questionnaire. We used reported symptoms to classify asthma control and categorised treatment following the 2020 GINA guidelines. We used multivariable logistic regression to study factors associated with treatment adjustment (step-up or down vs. no change).

Results: We included 551 children diagnosed with asthma (mean age 10 years, 37% female). At the clinical visit, most children were prescribed GINA Step 3 (35%). Compared to pre-visit treatment, 252 (47%) children remained on the same step, 227 (42%) were stepped-up and 58 (11%) were stepped-down. Female sex (aOR 1.61, 95% CI 1.05-2.47), poor asthma control (3.08, 1.72-5.54), and a lower Forced Expiratory Volume in the first second (FEV_1) Z-score (0.70, 0.56-0.86 per 1 Z-score increase) were independently associated with treatment step-up, and low FeNO (2.34, 1.23-4.45) with treatment step-down, with a marked heterogeneity between clinics.

Conclusion: In this tertiary care real-life study, we identified main drivers for asthma

treatment adjustment. These findings may help improve both asthma management guidelines and clinical practice.

Highlights box

1. What is already known about this topic?

Asthma guidelines recommend modifying asthma treatment according to symptom control and future risk of exacerbations or medication side effects. However, we know little about what drives paediatric pulmonologists to adjust treatment in children with asthma. (35/35 words)

2. What does this article add to our knowledge?

In this tertiary care real-life study, we found that lung function and asthma control played a key role for treatment step-up, and Fractional exhaled Nitric Oxide (FeNO) for stepping-down, with a marked heterogeneity between clinics. (35/35 words)

3. How does this study impact current management guidelines?

Understanding how asthma guidelines are followed in routine care may help to improve both recommendations and clinical practice. (18/35 words)

Key words: asthma management, children, clinical practice

List of Abbreviations

aOR: Adjusted odds ratio

BMI: Body Mass Index

CI: Confidence interval

FeNO: Fractional exhaled Nitric Oxide

$FEV_{1:}$ Forced Expiratory Volume in the first second

FVC: Forced Vital Capacity

GINA: Global Initiative for Asthma

ICS: Inhaled corticosteroids

LABA: Long-acting beta agonists

NICE: National Institute for Health and Care Excellence

OR: Odds ratio

SABA: Short-acting beta agonist

SD: Standard deviation

sIgE: Allergen specific IgE

SPT: Skin prick test

SPAC: Swiss Paediatric Airway Cohort

Manuscript: 3500 words

INTRODUCTION

Asthma treatment should be regularly adjusted to maintain a good control of symptoms with the minimum treatment possible (1-3). Asthma guidelines stratify treatment in steps, with increasing intensity, and advise to base treatment decisions on daily symptom control and future risk of exacerbations or medication side effects (1-3). Stepping up treatment may improve daily symptom control and reduce future risk of exacerbations. Stepping down treatment reduces costs and the risk of side effects associated with long-term use of anti-inflammatory treatment. However, other factors affect a doctor's management decision, including test results, comorbidities, personal preferences, treatment adherence, and environmental exposures such as tobacco smoke or aeroallergens. Asthma guidelines also recommend addressing these modifiable risk factors to reduce exacerbations and improve asthma control (1-3).

We know little about what drives doctors to adjust treatment in children with asthma (4, 5). Previous studies have reported that children who are younger, female, of black or Asian ethnicity, whose mothers have a lower education level, and with a milder disease tend to be prescribed lower treatment steps (6-9). However, most previous knowledge is based on reported asthma treatment by the patient, family, or prescribing physicians (5, 7-9). To have a better understanding of what doctors prescribe in a real-life setting, we need to look at treatment that has actually been prescribed. We used data from a clinical cohort embedded in routine care, to understand the factors that drive treatment adjustment in paediatric respiratory outpatient clinics.

METHODS

Study design and setting

This is a cross-sectional study nested in the Swiss Paediatric Airway Cohort (SPAC, registration number NCT03505216) that has already been described (10). Briefly, SPAC is a clinical cohort study embedded in the routine care of 6 respiratory outpatient clinics in Switzerland: Aarau, Basel, Bern, Luzern, St. Gallen and Zurich. All children aged 0-16 years seen at these clinics for respiratory problems such as wheeze, chronic cough, or exercise-induced symptoms were invited to participate. At recruitment, parents signed an informed consent form and completed a questionnaire, and we collected the clinical visit letter which is sent by the paediatric pulmonologist to the referring doctor. The study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkomission Bern 2016-02176) and we followed STROBE guidelines to report our findings (11).

Participants

For the current analysis, we included children of any age who had participated in SPAC between 1st July 2017 and 31st July 2019 who: (1) received a diagnosis of asthma in the outpatient clinic, (2) had signed the informed consent, and (3) completed the parental questionnaire. We excluded children who completed the questionnaire more than 3 months before the clinical visit, as children normally receive the appointment for the paediatric pulmonologist with the questionnaire, 1-3 months in advance. We excluded those who completed the questionnaire 2 weeks or more after the visit, as treatment changes prescribed at the visit might have modified the symptoms by then.

Data sources and definitions of exposures

To select the possible drivers of treatment adjustment, first we included the factors that the GINA 2019 guidelines recommend using to adjust treatment (12): symptom control, modifiable risk factors, comorbidities and treatment adherence (Figure E1). As modifiable risk factors we included lung function, exposure to tobacco smoke and allergen exposure if sensitised. For sensitisation we included allergy tests, and as comorbidities we included eczema, hay fever and body weight, measured as the Body Mass Index (BMI). We also included FeNO, which is still under debate whether it should be used to guide treatment in children (13). Finally, we included factors that should not drive treatment, but that have been previously associated with the prescribed step: age, sex, child's nationality as a proxy for ethnicity, mother's and father's education level and the clinic (6-9).

From the parental questionnaire, we collected information on respiratory symptoms, allergic diseases (hay fever and eczema), family history of allergic diseases, living conditions and sociodemographic data. Exposure to tobacco smoke was defined as either mother or father currently smoking. We used four respiratory symptoms in the last 12 months to classify symptom control: any daily activity limitations, any night-time symptoms, any missed school-days and more than 3 attacks of wheezing. We classified symptom control into well (no symptoms), partly (1-2 symptoms present) or uncontrolled (3-4 present).

From the clinical visit letter and test reports we extracted information on body weight, height, diagnosis, clinical history, physical examination, FeNO, spirometry, skin prick test (SPT), allergen specific IgE (sIgE) and treatment adherence. We used weight and height to calculate BMI Z-scores using references values from the World Health Organisation (14). We classified FeNO into 'high' using each clinics' limits of normality because they used different

devices, as described previously (15). The FeNO cut-offs varied from 10ppb when using an online method to 20-25ppb when using an offline method. We also tested FeNO as a continuous variable (log-transformed) and divided into 4 equally distributed groups. We transformed Forced Expiratory Volume in the first second (FEV_1) and Forced Vital Capacity (FVC) into Z-scores using Global Lung Initiative standards (16). We estimated FEV_1 increase after a short-acting beta agonist (SABA) using the formula (post- FEV_1 - pre- FEV_1 / pre- FEV_1) x 100%, and defined a 12% increase or more as 'bronchodilator reversibility' (12). SPT was defined as positive if the mean wheal size for any allergen was 3mm or more, and sIgE if levels were 0.35 kU/L or more. We defined 'positive allergy tests' as having either a positive SPT or a positive sIgE. Treatment adherence was classified as 'good' or 'poor' as reported in the clinical visit letter by the treating doctor, or as 'not reported' when it was not mentioned. No objective measurements were used for treatment adherence assessment, and we defined as 'poor' when the doctor reported that the child did not take all the prescribed doses. We did not collect information on treatment action plans as these were not routinely used, were not standardised across centres and were handed over directly to the families.

Data sources and definitions of outcomes

We collected the information on the previous and current treatment prescribed from the clinical visit letter. We then classified it into steps according to the GINA 2020 asthma guidelines (Table E1) (12). Treatments not recommended by GINA 2020 guidelines were classified as 'other'. We then used the information on previous and current asthma treatment to define the treatment decision as 'step-up' (increased the treatment intensity), 'step-down' (decreased the treatment intensity) or 'no change' (remained the same). We also classified as 'step up' children that were started on asthma treatment for the first time,

as 'step-down' those that were prescribed to stop treatment completely and as 'no change' those that changed the specific drug prescribed for preference reasons but remained on the same step.

Statistical Analysis

We studied which factors drive asthma treatment adjustment using two multivariable logistic regression models: one comparing 'step-down' to 'no change' and one comparing 'step-up' to 'no change'. We excluded the children who had no information about their previous asthma treatment (before the clinical visit, N= 14). We selected the variables in the final model using Collett's method (17) to produce a final list of non-collinear predictors, based on their influence on the other variables' coefficients and a p-value threshold of 0.2. We forced age, sex and clinic into the model when possible. We performed the analysis when there were at least 500 children with asthma recruited, to allow for 10 events per non-collinear predictor for each treatment adjustment (18), assuming that at least 20% of cases would either step-up or down.

We performed multiple imputation for variables with missing values using the "mi"(19) procedure in Stata with 20 iterations. The imputation models included all variables selected and the outcome of interest (20). We presented the results of the multivariable regression models using multiple imputation in the main results. We performed two sensitivity analyses. First, we did a complete-case analysis, restricting to children who had information on all predictors, as some of the missing values were not missing at random. This was especially the case for spirometry and FeNO that were missing when the treating doctor decided not to perform them, or when they could not be performed. The number of available data for each variable is included in Table 1. Second, we excluded children under 6 years of age as the management of these children may vary from school-aged children. We

used STATA 15 to perform the statistical analysis and reported the Odds Ratios (OR) with their 95% confidence intervals (CI).

RESULTS

Among 2561 children invited, 1537 agreed to participate and completed the parental questionnaire (Figure 1). 551 were diagnosed with asthma and included in the study. 203 (37%) were female, mean age was 10 years (SD 3.5), 147 (28%) were well controlled and 159 (30%) had more than 3 asthma exacerbations during the previous year (Table 1). Most children (488, 93%) were referred for suspected asthma or wheeze, of whom 50 (10%) were referred because of difficulties in attaining good asthma control or to ask for guidance with the treatment (data not shown). Other referral reasons were allergic rhinoconjunctivitis (10, 2%), recurrent respiratory infections (5, 1%), exercise induced symptoms (4, 1%), chronic cough (3, 1%), and other reasons (13, 2%). Adherence was mentioned in less than a half of the clinical visit letters. An allergy test was performed in 216 children and was positive in 148 (69%), FeNO was measured in 512 and in 264 (52%) defined as high, and lung function tests were done in 436, with a mean FEV_1 Z-score of -0.54 and a mean FEV_1/FVC of 0.84.

At the clinical visit, 80% of the children were prescribed inhaled corticosteroids (ICS), and half of these were combined with long-acting beta agonists (LABA) (Table E2). Most children were prescribed Step 3 (194, 35%), followed by Step 4 (115, 21%), Step 1 (108, 20%), Step 2 (91, 17%), with only 6 (1%) on Step 5, a further 17 (3%) were prescribed no treatment and 20 (4%) were prescribed treatment not included in the GINA 2019 recommendations for the child's age (Figure 2). Of the 537 children that had information on their previous treatment, most had no change in their treatment intensity at the clinical visit (252, 47%), 227 (42%)

were stepped-up and 58 (11%) were stepped down (Table 1 and Figure 2). Children on a previous step 1 or 4 were mostly not changed, while children on a previous step 2 were mostly stepped up, and children on step 3 were mostly not changed or stepped up (Figure 2). Children with a worse asthma control were more frequently stepped-up and were also more frequently prescribed a higher asthma treatment step (Figure 3).

Factors associated with stepping down treatment were clinic (Centre C had a higher odd of stepping down than Centre A, aOR 2.62, 95% CI 1.10-6.22) and a low FeNO (aOR 2.34, 95% CI 1.23-4.45) (Figure 4a and Table E3). All other factors were not associated with stepping down treatment (Table E3).

Factors associated with stepping up treatment were female sex (aOR 1.61, 95% CI 1.05-2.47), clinic (Centre B had a higher odd of stepping up than Centre A, aOR 1.93, 95% CI 1.09-3.43) a poor asthma control (vs. well controlled, aOR 3.08, 95% CI 1.72-5.54), and a lower FEV_1 Z-score (aOR 0.70, 95%CI 0.56-0.86 per 1 Z-score increase) (Figure 4b and Table E4). In the univariable analysis, of the 4 items used to define asthma control, having had more than 3 wheezing attacks in the last 12 months, was the most strongly associated to stepping up (aOR 2.73, 95% CI 1.81-4.12) (Table E4). All other factors were not associated to stepping up treatment, including FeNO both as a continuous (log-transformed) or dichotomous (high vs. low) variable (Table E4).

The complete-case analysis (Tables E5 & E6) resulted in some slight differences in the odds ratios of the centres, but the direction of the associations remained the same and most results did not vary, especially not the associations with lung function and FeNO. Also, the second sensitivity analysis, where we excluded children under 6 years old, showed very similar findings as the main analysis including all age groups (Tables E7 & E8). To highlight, the effect of female sex did vary slightly in the sensitivity analyses. It was significantly

associated to treatment step-down in the complete case analysis with (aOR 2.02, 95% CI 1.06-3.86) and without (aOR 2.04, 95% CI 1.03-4.03) children under 6 years old, while this was not the case in the main analysis. For treatment step-up, female sex was less strongly associated in the complete case analysis.

DISCUSSION

In this cross-sectional study embedded in routine care, we found that 47% of children with asthma seen at paediatric respiratory outpatient clinics in Switzerland did not have their treatment modified, 42% were stepped up and only 11% were stepped down. Most children were prescribed a step 3 (35%) or 4 (21%) at the respiratory outpatient clinic. The main drivers for treatment step-up were female sex, uncontrolled asthma and a lower FEV_1. The main driver for treatment step-down was a low FeNO. There was marked heterogeneity between clinics, with some clinics more prone to stepping up, and others to stepping down.

Strengths and limitations

This study presents the real-life prescribing practices of paediatric pulmonologists for children with asthma in Switzerland. It is a large multicentre study with a heterogeneous sample of children with different degrees of asthma severity and control. We also had information on many different respiratory symptoms collected in a standardised way through a questionnaire, as well as objective tests results and information from the treating paediatric pulmonologist such as the child's adherence to treatment. However, this study also has limitations. First, as it is embedded in routine care, objective tests were only performed based on the doctor's indication resulting in some missing data and hampering the possibility of studying tests that are not frequently performed such as blood eosinophils.

However, for the included measurements, such as lung function and FeNO, only few children had missing data and the findings were comparable in the analysis using multiple imputation for missing data and the complete-case analysis. This was also the case for tests that depend on the clinical history such as allergy tests, performed in 40% of the children for the specific clinical visit. Second, the questionnaire that the families completed for the study was not disclosed to the treating paediatric pulmonologists who based their decisions on treatment adjustment on their own specific questions and the answers they obtained during the visit. These may have differed from the answers we obtained through the questionnaire. Third, the results are only representative for the German-speaking region of Switzerland. Fourth, the small proportion of children that were stepped down limited the number of factors that we could include in the multivariable model. Most children were referred back to their paediatrician once their asthma was well controlled, and it will be the paediatrician who will step-down the treatment following the paediatric pulmonologist's recommendations.

Findings in relation to previous studies

Little is known about factors that drive paediatric pulmonologists to adjust asthma treatment. Two studies have investigated drivers of treatment adjustment among asthma specialists, but only for adult patients (4, 21). Others assessed which information paediatricians used to assign asthma treatment in primary care (5, 22). Okelo et al. used case vignettes (a short written summary of a case) of children with asthma to assess this. They found that asthma control, recent hospitalisation for asthma and an asthma that bothered the parents were the main drivers for both stepping up and stepping down among paediatricians (5). Wheezing on examination also guided treatment step-up, while symptom stability guided treatment step-down (5). These factors are related to daily symptom control and the risk of severe attacks (previous hospitalisation). In our study, we found that asthma

control was an important driver for stepping-up in children, but not for stepping down. Case vignettes allow to control for unmeasured confounders, but they do not study actual practice. Also, the authors did not assess the effect of other factors such as the child's treatment adherence, objective tests results, age, sex, or the parent's education level (5). Yawn et al. used clinical records to assess factors associated with asthma treatment adjustment in primary care (22). They found that stepping down was much rarer than stepping up and that the most common reason for stepping up was an asthma exacerbation (22). Asthma exacerbations during the previous year were included in our asthma control definition, and when looking at each item separately in the univariable analysis, number of exacerbations was the strongest item associated with treatment step-up.

Asthma guidelines recommend assessing adherence before adjusting treatment. Several studies reported poor adherence to controller treatment as a frequent barrier to obtain adequate symptom control in children (23-25). In our study, adherence was not associated with stepping up or down, but adherence was only mentioned in 48% of the clinical visit letters. There was no evidence that treatment was affected by socio-economic factors such as the child's nationality or parents' education. We found that treatment of girls was more often changed than boys, though the association was not consistent across the different analysis. This could reflect an inadequate management of girls with asthma in primary care, with girls being both under and overtreated compared to boys with the same degree of symptom control. Previously, a population-based study reported that girls might be undertreated in Switzerland (26).

Biomarkers such as FEV_1 and FeNO played an important role in treatment adjustment decisions. FeNO values have been reported to drive treatment adjustment in adult patients (27, 28). We found that paediatric pulmonologists used FeNO to step-down treatment but

not to step-up. In adults, a recent meta-analysis found that the use of FeNO to guide treatment step-down reduced ICS use without increasing the risk of exacerbations (29), but further research is needed. In children, the role of FeNO to monitor asthma and adjust treatment is controversial. The recent NICE guidelines(3) and the GINA guidelines(1) do not recommend FeNO-guided treatment, though it may reduce exacerbation rates(13). Despite this, FeNO is often measured, as it may be a helpful surrogate of eosinophilic airway inflammation in otherwise asymptomatic children at risk of asthma attacks when reducing ICS dose (30). However, it remains important to use clinical and anamnestic information, such as symptom control, to guide treatment step-down and not FeNO alone. In our study, a lower FEV_1 was the most important driver of treatment step-up but did not affect treatment step-down. Also in a US study, spirometry results influenced management decisions of paediatric pulmonologists in 15% of the evaluated visits, contributing to stepping-up 75% of these (31). According to asthma guidelines, lung function should be regularly assessed to adjust treatment(1-3), because poor lung function has been associated with a greater risk of asthma exacerbations(32-34) and for persistent airflow limitation(35-37).

Implication for practice and future research

Asthma management guidelines should consider current prescribing practices of paediatric pulmonologists when advising on asthma treatment adjustments. Recommendations obtained from randomised controlled trials done on selected populations, under controlled circumstances and high resources, may be difficult to implement in routine care. Also, doctors may start prescribing certain treatments before they are recommended in guidelines, as it may take years to implement research findings into clinical guidelines. Real prescribing patterns can only be assessed in observational clinical cohorts like SPAC. Our study suggests that paediatric pulmonologists may apply study findings before they are

recommended in asthma guidelines, as they used FeNO to decide treatment step-down and had started prescribing ICS/LABA as needed before it was recommended for Step 1 in the 2019 GINA guidelines. Some recommendations from asthma guidelines may be difficult to implement in clinical practice. This is the case with the assessment of treatment adherence, which was rarely reported in the hospitals participating in SPAC. It would be desirable to have less costly and broadly available smart inhalers to assess adherence easily and accurately in children with asthma. Our study was done in tertiary care. We think that similar studies should also be done in primary care to investigate what drives general paediatricians to adjust asthma treatment. Most children with asthma are managed in primary care, and the factors driving treatment adjustment in primary care may differ. The marked heterogeneity between the participating clinics reflects relevant differences in clinical practices. Standardising asthma treatment in children is important to assure an adequate management. Updated national guidelines with the contribution of all paediatric pulmonology services may help in attaining a standardised and updated management.

Conclusion

In conclusion, this national study conducted in a real-life setting found that lung function and level of asthma control play a key role in asthma treatment step-up while FeNO is currently the main driver of treatment step-down. Asthma treatment adjustment practices differed broadly between clinics. Understanding how asthma treatment is adjusted in routine care may help to improve recommendations and clinical practice.

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Authors' contributions: CE Kuehni and C Ardura-Garcia conceptualised and designed the current analysis, and they assume responsibility for all content of the manuscript. J Barben, A Jochmann, A Jung, D Mueller-Suter, N Regamey, F Singer supervised data collection. ESL Pedersen, MC Mallet, CCM de Jong and C Ardura-Garcia collected and prepared data. C Ardura-Garcia analysed the data and drafted the manuscript. All authors critically revised the manuscript and approved the final manuscript as submitted.

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FIGURE LEGENDS

Figure 1: Flowchart of included participants

SPAC: Swiss Paediatric Airway Cohort

Figure 2: Change in asthma treatment step after respiratory outpatient clinical visit for children participating in the SPAC study (N=537)

'Other' includes: Any dose ICS-LABA and short courses (4-6 weeks) of low dose ICS for children under 6 years old. As-needed ICS-LABA for children 6-11 years old. Green arrows indicate treatment step-down, blue arrows indicate no change and red arrows indicate step-up. The black arrow indicates change from Step 4 to 'Other', where we cannot assess if it is a step-up or step-down.

Figure 3: Asthma treatment adjustment (A) and treatment step proposed (B) by paediatric pulmonologists for children with different levels of asthma control at presentation (well, partly and uncontrolled) (N=537)

'Other' includes: Any dose ICS-LABA and short courses (4-6 weeks) of low dose ICS for children under 6 years old. As-needed ICS-LABA for children 6-11 years old.

Figure 4: Factors associated with stepping down (A) and stepping up (B) asthma treatment by paediatric pulmonologists, using multiple imputation for missing values (N= 537)

BMI: Body Mass Index; FeNO: Fraction of exhaled nitric oxide; FEV_1: Forced expiratory volume in the first second. *Asthma control during the last 12 months as reported by parental questionnaire before the respiratory outpatient visit ** Adherence to treatment as reported in outpatient visit letter #: Definition of low FeNO depended on technique used and specified cut-offs for each centre 1: Adjusted for all the variables included in the multivariable model, 2: Adjusted for all the variables in the multivariable model and also mother's education

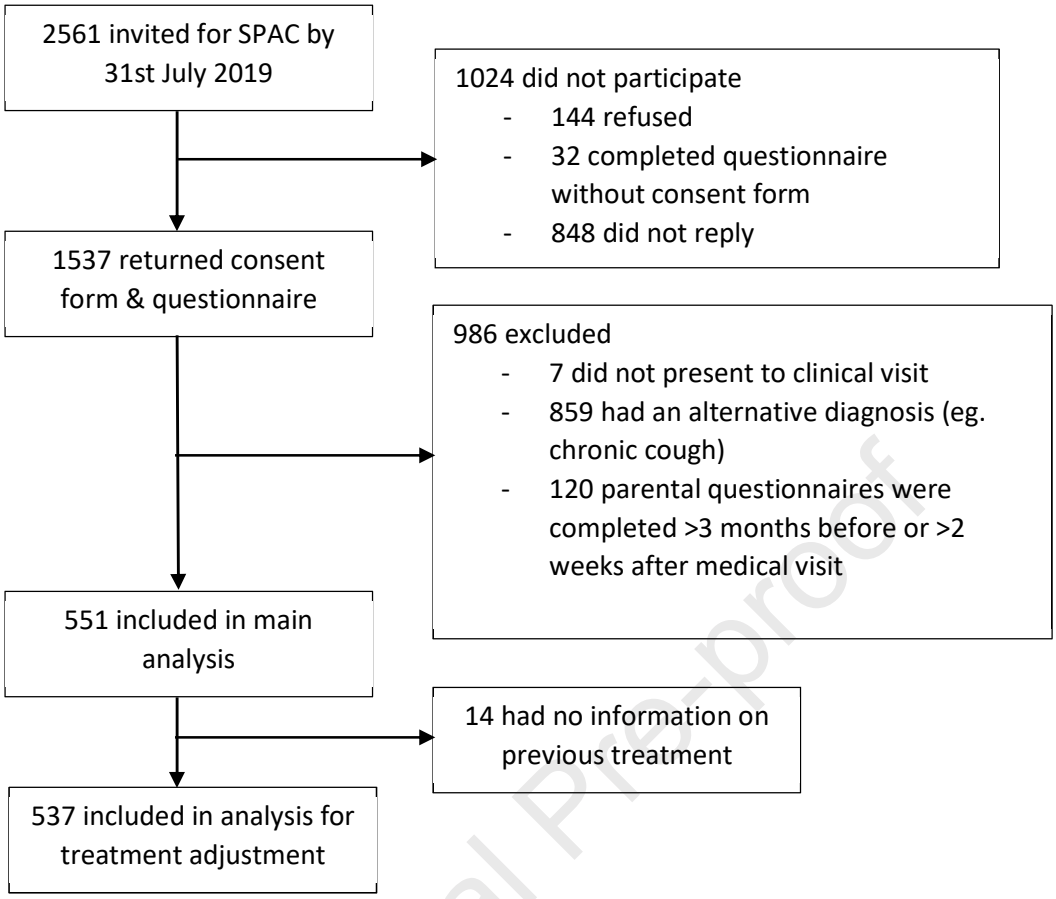
579 Table 1: Characteristics of children included in the study: whole population and stratified by asthma
580 treatment modification at the respiratory outpatient visit

	All N = 551 n (%)	Step-down N= 58 n (%)	No change N= 252 n (%)	Step-up N= 227 n (%)
Sociodemographics				
Female sex	203 (37)	25 (43)	81 (32)	90 (40)
Age, years (mean, SD)	10.1 (3.5)	9.7 (3.2)	10.6 (3.5)	9.7 (3.3)
Clinic				
Centre A	154 (28)	15 (26)	80 (32)	56 (25)
Centre B	149 (27)	17 (29)	47 (19)	77 (34)
Centre C	93 (17)	2 (3)	15 (6)	29 (13)
Centre D	58 (11)	14 (24)	28 (11)	15 (7)
Centre E	93 (17)	7 (12)	58 (23)	28 (12)
Centre F	49 (9)	3 (5)	23 (9)	23 (10)
Swiss nationality	464 (84)	52 (90)	211 (84)	190 (83)
Highest mother's education level (N=536)				
Primary	42 (8)	3 (5)	15 (6)	24 (11)
Secondary	292 (55)	31 (55)	125 (51)	127 (57)
Tertiary	202 (38)	22 (39)	104 (43)	71 (32)
Highest father's education level (N=526)				
Primary	36 (7)	4 (7)	13 (5)	18 (8)
Secondary	260 (49)	30 (54)	111 (46)	112 (52)
Tertiary	239 (44)	22 (39)	117 (49)	86 (40)
Exposure to tobacco smoke (N= 531)	172 (32)	21 (37)	65 (27)	82 (38)
Comorbidities				
BMI Z Score (mean, SD) (N= 546)	0.26 (1.2)	0.39 (1.2)	0.23 (1.2)	0.26 (1.3)
Eczema doctor's diagnosis (N= 493)	185 (38)	16 (33)	84 (37)	80 (39)
Hay fever doctor's diagnosis (N= 542)	271 (50)	24 (42)	137 (55)	105 (47)
Asthma characteristics				
Asthma control last 12 months* (N= 519)				
Well controlled	147 (28)	22 (42)	82 (35)	43 (20)
Partly controlled	207 (40)	17 (33)	108 (46)	77 (36)
Uncontrolled	165 (32)	13 (25)	47 (20)	96 (44)
Exercise-induced respiratory symptoms (N=534)	375 (70)	39 (72)	165 (67)	160 (73)
Adherence to asthma treatment** (N=531)				
Good	176 (33)	22 (41)	85 (35)	64 (29)
Poor	81 (15)	7 (13)	47 (19)	26 (12)
Not mentioned	274 (52)	25 (46)	110 (45)	133 (60)
GINA treatment step prescribed at the visit$				
No treatment	17 (3)	3 (5)	10 (4)	0
Step 1	108 (20)	16 (28)	77 (31)	13 (6)
Step 2	91 (17)	13 (22)	39 (15)	39 (17)
Step 3	194 (35)	16 (28)	77 (31)	98 (43)
Step 4	115 (21)	6 (19)	38 (15)	67 (30)
Step 5	6 (1)	1 (2)	5 (2)	5 (2)
Other	20 (4)	3 (5)	6 (2)	5 (2)
Diagnostic Tests				
Positive allergy test& (N= 216)	148 (69)	13 (65)	54 (70)	78 (69)
High FeNO# (N= 512)	264 (52)	16 (30)	116 (50)	125 (59)
FEV1 Z score (mean, SD) (N=436)	-0.54 (1.2)	-0.20 (1.0)	-0.36 (1.2)	-0.80 (1.1)
FEV1/FVC (mean, SD) (N=414)	0.84 (0.1)	0.86 (0.08)	0.84 (0.09)	0.83 (0.08)
% FEV1 bronchodilator increase (mean, SD) (N=272)	9.3 (9.6)	6.1 (6.1)	7.6 (8.7)	11.4 (10)

581 SD: standard deviation; BMI: Body Mass Index; FeNO: Fraction of exhaled nitric oxide; FEV1: Forced expiratory volume in the first second;
582 FVC: Forced vital capacity; SABA: Short-acting beta-agonists; ICS: inhaled corticosteroids; LABA: long-acting beta-agonists; GINA: Global
583 initiative for asthma. *During the last 12 months before the respiratory outpatient visit ** Adherence to previous treatment as reported in
584 outpatient visit letter #: Definition of high FeNO depended on technique used and specified cut-offs for each centre: 10ppb when using an

585 online method and 20-25ppb when using an offline method. $ Specific treatment by age groups for each step described in Table E1. &:
586 Positive Skin prick test or allergen specific IgE for any allergen.

Figure 1: Flowchart of included participants



SPAC: Swiss Paediatric Airway Cohort Study

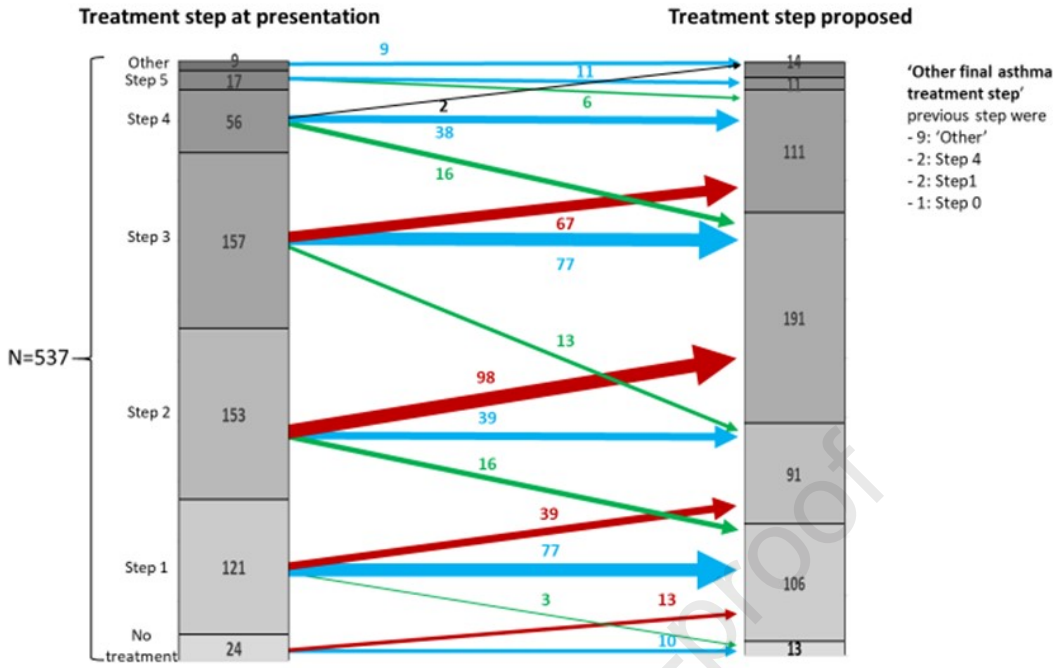
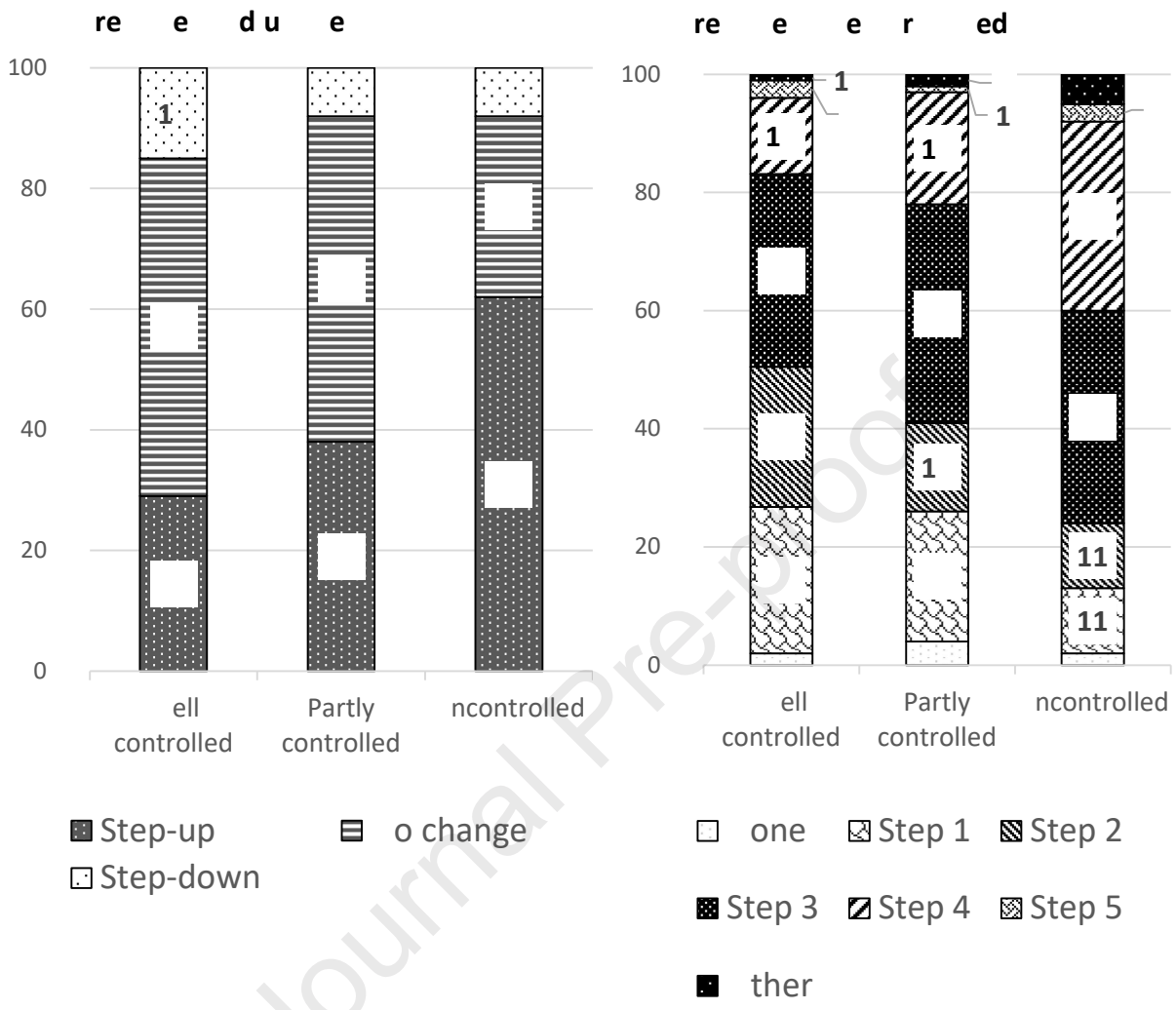


Figure 3: Asthma treatment adjustment (A) and treatment step proposed ( ) by paediatric pulmonologists for children with different levels of asthma control at presentation (well partly and uncontrolled) (537)



ther includes: Any dose CS- A A and short courses (4-6 weeks) of low dose CS for children under 6 years old. As-needed CS- A A for children 6-11 years old.