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Predictors of asthma control differ from predictors of asthma attacks in children: The Swiss Paediatric Airway Cohort

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Abstract

Background: It is unclear if predictors of asthma attacks are the same as those of asthma symptom control in children.

Objective: We evaluated predictors for these two outcomes in a clinical cohort study.

Methods: The Swiss Paediatric Airway Cohort (SPAC) is a multicentre prospective clinical cohort of children referred to paediatric pulmonologists. This analysis included 516 children (5–16 years old) diagnosed with asthma. At baseline, we collected sociodemographic information, symptoms, personal and family history and environmental exposures from a parental baseline questionnaire, and treatment and test results from hospital records. Outcomes were assessed 1 year later by parental questionnaire: asthma control in the last 4 weeks as defined by GINA guidelines, and asthma attacks defined as any unscheduled visit for asthma in the past year. We used logistic regression to identify and compare predictors for suboptimal asthma control and asthma attacks.

Results: At follow-up, 114/516 children (22%), reported suboptimal asthma control, and 114 (22%) an incident asthma attack. Only 37 (7%) reported both. Suboptimal asthma control was associated with poor symptom control at baseline (e.g. ≥1 night wheeze/week OR: 3.2; 95% CI: 1.7–6), wheeze triggered by allergens (2.2; 1.4–3.3), colds (2.3; 1.4–3.6) and exercise (3.2; 2–5), a more intense treatment at baseline (2.4; 1.3–4.4 for Step 3 vs. 1), history of preschool (2.6; 1.5–4.4) and persistent wheeze (2; 1.4–3.2), and exposure to tobacco smoke (1.7; 1–2.6). Incident asthma attacks were associated with previous episodes of severe wheeze (2; 1.2–3.3) and asthma attacks (2.8; 1.6–5 for emergency care visits), younger age (0.8; 0.8–0.9 per 1 year) and non-Swiss origin (0.3; 0.2–0.5 for Swiss origin). Lung function, exhaled nitric oxide (FeNO) and allergic sensitization at baseline were not associated with control or attacks.

Study registered at clinicaltrials.gov (identifier NCT03505216) on 23rd April 2018.

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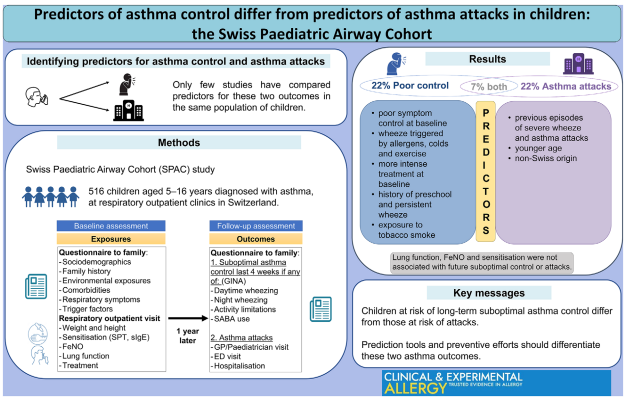
Conclusion: Children at risk of long-term suboptimal asthma control differ from those at risk of attacks. Prediction tools and preventive efforts should differentiate these two asthma outcomes.

KEYWORDS
asthma attacks, asthma control, children, clinical practice



GRAPHICAL ABSTRACT

Children at risk of poor asthma control are different to those at risk of asthma attacks, with only 7% at risk for both. Lung function, FeNO, and sensitisation at baseline were not associated with suboptimal control or asthma attacks 1 year later. Prediction tools and preventive efforts should differentiate these two asthma outcomes.

1 | INTRODUCTION

Disease control, defined as the absence of recurrent symptoms affecting sleep or daily activities, and prevention of severe attacks leading to emergency healthcare consultations, is the ultimate goal of asthma treatment.[1] Less than 50% of children achieve adequate disease control.[2–6] Identifying children at risk of poor symptom control and asthma attacks is important in preventing negative long- and short-term consequences. Poor symptom control limits daily activities and quality of life, while asthma attacks may cause anxiety,[7] high individual and healthcare costs,[6,8] and carry a risk of death and long-term damage such as loss of lung function.[9] Symptom control may be improved, and asthma attacks prevented with closer follow-up, avoidance of triggers, improvement of inhaler technique, treatment adherence, and asthma treatment adjustments.[10] However, it remains unclear how children at risk of poor symptom control and asthma attacks can be identified early, as there are currently no prediction tools for use in clinical care.

Several studies have identified predictors of long-term symptom control or predictors of asthma attacks.[3,5,10–19] However, they had limitations. First, they did not always use prospective data. Most studies on symptom control in children are cross-sectional surveys,[3,5,18,19] limited by recall bias. On the other hand, studies describing predictors of asthma attacks are multiple, and primarily prospective in design.[17,20] Some authors have combined single predictors into prediction scores to identify children at risk of asthma attacks, but none of the scores has been implemented into clinical practice.[11–16] Second, most did either look at predictors for poor symptom control or at predictors for asthma attacks, but not both. Only two prospective studies assessed predictors for symptom control and attacks separately in the same group of children. One used data from a US randomised controlled trial (RCT),[21] the other came from a UK primary care setting,[22] and both included a relatively small selection of respiratory symptoms as potential predictors. Both studies found differences in the predictors for the two outcomes, which may be due to differences in underlying pathogeneses. Poor symptom control is associated with increased airflow limitation and diurnal variability, and responds well to short-acting β_2-agonists (SABA).[23–26] Asthma attacks may still occur despite good symptom control, are associated with increased airway inflammation, decreased SABA responsiveness, and minimal diurnal variability.[24,25,27] Experts have recommended to assess and manage these two different outcomes as individual treatable traits,[24] and to study them separately.

Key messages

- Children at risk of long-term suboptimal asthma control differ from those at risk of attacks.
- Prediction tools and preventive efforts should differentiate these two asthma outcomes.
- Lung function, FeNO and sensitisation were not associated with future suboptimal control or attacks.

We wanted to investigate if children at risk of long-term suboptimal symptom control are the same as those at risk of asthma attacks. We therefore compared predictors for these two outcomes in a longitudinal study of children treated by paediatric pulmonologists for asthma.

2 | METHODS

2.1 | Study design and setting

The Swiss Paediatric Airway Cohort (SPAC) is an ongoing prospective clinical cohort study embedded in the routine care of six paediatric respiratory outpatient clinics across Switzerland (Aarau, Basel, Bern, Luzern, St. Gallen, Zurich). Procedures have been described elsewhere.[28] The study is registered at clinicaltrials.gov (identifier NCT03505216). In summary, children of any age referred for common respiratory problems such as asthma, chronic cough or exercise induced problems, are invited to participate. Parents complete a baseline questionnaire on sociodemographics, environmental exposures, personal and family history, respiratory symptoms and treatment. Data on diagnoses, prescribed treatments and test results are collected from electronic health records. Children are followed up prospectively through yearly parental questionnaires and continuous collection of clinical data if new clinical visits take place. The study protocol did not include any scheduled clinical visits, and these took place depending only on the child's paediatric pneumologist's or paediatrician's criteria. For these analyses we included only clinical data from the baseline visit. The study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkomission Bern 2016-02176) and the parents signed an informed consent form. We followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to report our findings.

2.2 | Participants

This analysis included children aged 5 years and older at recruitment, who were diagnosed with asthma (suspected or confirmed) by the paediatric pulmonologist and had completed the baseline and first year follow-up questionnaire by 31 July 2020. We excluded children with a diagnosis of bronchopulmonary dysplasia.

2.3 | Definitions of predictors

We selected potential predictors of poor asthma control and asthma attacks based on the literature and discussions with the paediatric pulmonologists working in the SPAC centres. The selected predictors included sociodemographic information, environmental exposures, family history of allergic diseases, comorbidities and respiratory symptoms from the baseline questionnaire, and treatment, lung function, airway inflammation and allergic sensitisation from the clinical data.

Sociodemographic information included age, sex and child's country of birth and level of parental education. Environmental exposures included exposure to tobacco smoke, pets, farm animals and mould. For family history we used parental hay fever and asthma. As comorbidities we included hay fever, eczema and body mass index (BMI). We used weight and height from the clinical visit to estimate BMI and transformed it into Z-scores using references values from the World Health Organisation.[29] Respiratory symptoms included preschool and persistent wheeze, activity limitations, night-time symptoms, missed school days, number of wheeze exacerbations, exercise induced wheeze, wheeze triggers (infections, exercise and allergens), night cough, dyspnoea, severe wheeze, unscheduled visits to their doctor or the emergency department (ED), and hospitalisations in the last 12 months. Exact definitions and questions used for each predictor are described in Table S1. We classified the treatment prescribed into treatment steps according to 2021 Global Initiative for Asthma (GINA) guidelines.[1]

2.4 | Physiological measurements

The objective tests were performed as per the treating physician's criteria and not solely for the study. We collected information on: forced expiratory volume in the 1st second (FEV_1), forced vital capacity (FVC), and forced mid-expiratory flow (FEF25-75) from spirometry; Fractional of exhaled Nitric Oxide (FeNO), and allergic sensitization to aeroallergens (skin prick test (SPT) or allergen specific immunoglobulin E (IgE) in serum). Trained lung function technicians performed spirometry testing following the ERS/ATS recommendations.[30,31] We calculated FEV_1, FEV_1/FVC and FEF25-75 Z-scores using Global Lung Initiative reference equations.[32] We estimated the increase in FEV_1 after applying SABA using the formula: (post-FEV_1−pre-FEV_1/pre-FEV_1)×100%. We defined bronchodilator reversibility based on ERS recommendations (≥12% or ≥200 mL increase). FeNO was measured using different devices depending on the centre. We classified the FeNO value into 'high' and 'normal', and we defined 'high' as >20 parts per billion (ppb) if an online method was used and >10 ppb if an offline method was used. We also used the raw FeNO value in ppb excluding those measured by an offline method (42/463, 9%). Sensitization to aeroallergens was defined as a wheal >3 mm in the SPT or specific IgE > 0.35 kU/L.

2.5 | Definitions of outcomes

Outcomes were assessed 1 year later by postal questionnaire to parents. We defined suboptimal asthma control following the GINA guidelines[4] (Table S2) using answers on night wakening due to wheeze, daytime wheezing, disturbance of daily activities, and the need for SABA over a preceding 4-week period. GINA guidelines define well-controlled asthma if they answer 'no' to all 4 questions, partly controlled if they answer 'yes' to 1–2 questions, and uncontrolled if they answer 'yes' to 3 or more questions. We defined suboptimal control

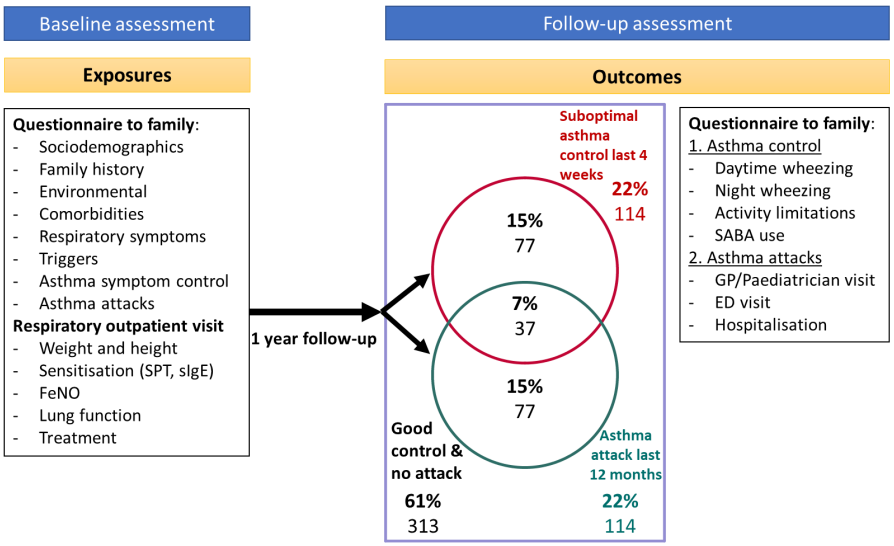


FIGURE 1 Study design and Venn diagram showing the overlap between children with suboptimal asthma control after the 1 year follow-up and those that had suffered an asthma attack ($N = 516$). Twelve children of the 516 could not be classified as having good control and no asthma attacks or not, as they did not answer the question on asthma attacks at follow-up. These 12 children are not included in this figure. ED, emergency department; FeNO, Fraction of exhaled nitric oxide; GP, general practitioner; SABA, short-acting beta-agonist; sIgE, allergen specific immunoglobulin E; SPT, Skin prick test.

when children were partly controlled or uncontrolled. We defined asthma attacks using the ATS/ERS 2009 statement[33] definition: a worsening of asthma symptoms that requires emergency care, including an unscheduled urgent visit to a GP or paediatrician, a visit to a hospital's ED or a hospitalisation, in the last 12 months (Table S2). In our study the last 12 months refers to the period between the baseline visit and the first year follow-up questionnaire (Figure 1).

2.6 | Statistical analysis

We described the proportion of children with suboptimal asthma control 1 year later, the proportion that suffered an asthma attack during this year, and the overlap between these two groups of children. We then described the characteristics of these children and presented the proportions for dichotomous variables and the median and interquartile range (IQR) for continuous variables with non-normal distribution. We explored the predictors for each outcome (suboptimal asthma control and asthma attacks) using logistic regression. We included all the exposures described above and adjusted them for age and sex. We presented odds ratios (OR) with 95% confidence intervals (95% CI). Missing values were excluded from the analysis. Information available per variable is shown in Table 1. We used STATA version 14 for statistical analysis.

3 | RESULTS

By July 2019, 2516 children had been invited to participate in the SPAC study and 1569 (62%) had agreed (Figure S1). Of these, 516 had completed the baseline and follow-up questionnaires, were 5 years and older and had received an asthma diagnosis at the paediatric pulmonologist's visit. Two thirds were male and the median age was 9 years (IQR, 6–12; Table 1). At baseline, one third (174/506) had suffered an asthma attack (unscheduled visit or hospitalisation for acute asthma). Of the predictors related to asthma control at baseline, 317 (63%) had at least one wheeze exacerbation, 259 (51%) reported activity limitations, and 167 (32%) reported night wakening due to wheeze, during the previous year (Table 1; Table S3). Over two thirds (292, 70%) were sensitised to an aeroallergen and half (258, 49%) presented a high FeNO value at baseline. Among the 325 children with a bronchodilator reversibility test, one third (105, 31%) demonstrated a significant bronchodilator reversibility (Table 1).

One year later, 114 (22%) reported suboptimal asthma control in the last 4 weeks, 114 (22%) had suffered an asthma attack in the last year and 313 (61%) reported good control and no attacks (Figure 1). The overlap between children with suboptimal control and those with attacks was small (7% of total population).

Looking at personal and family predictors, suboptimal asthma control was predicted by exposure to tobacco smoke (OR 1.67, 95% CI: 1.07–2.62), while asthma attacks were predicted by younger age (OR 0.84, 95% CI: 0.78–0.91 per 1 year increase) and non-Swiss nationality (OR 0.31, 95% CI: 0.18–0.53 for Swiss nationality). Absence of a paternal history of asthma was associated with both outcomes, though only statistically significantly for asthma attacks (OR 0.45, 95% CI: 0.22–0.93; Table 1; Figure 2; Table S4). Pet ownership, farm animals and humidity or mould in the house were not associated with either outcome (Table S7).

Among respiratory symptoms and healthcare utilisation at baseline (Table 1; Figure 3; Table S5), limitation of activities, night wheeze and severe wheeze were associated with both outcomes, but more strongly with suboptimal control. Predictors only associated with suboptimal asthma control were preschool wheeze (OR 2.58, 95% CI: 1.53–4.35), persistent wheeze (OR 2.07, 95% CI: 1.35–3.16), number of wheezing episodes (OR 4.01, 95% CI: 1.64–9.80 for >12 episodes vs. none), school days lost (OR 2.64, 95% CI: 1.20–5.80 for <10 days lost vs. none), exercise induced symptoms (OR 2.02, 95% CI: 1.22–3.34), wheeze triggered by allergens (OR 2.2, 95% CI: 1.4–3.3), colds (OR 2.3, 95% CI: 1.4–3.6) and exercise (OR 3.2, 95% CI: 2–5), and dyspnoea episodes (OR 1.69, 95% CI: 1.28–2.23). Previous asthma attacks were more strongly associated with asthma attacks at follow-up.

TABLE 1 Children's characteristics at baseline, overall and stratified by outcome 1 year later.

	All (*N* = 516)	Suboptimal asthma control last 4 weeks of follow-up (*N* = 114)	Asthma attack during 1 year follow-up (*N* = 114)	Good control & no asthma attack at follow-up (*N* = 313)
Sociodemographics				
Female sex	223 (35)	57 (40)	61 (35)	119 (34)
Age, years (median, IQR))	9 (6–12)	9 (6–12)	6 (4–10)	10 (7–13)
Swiss nationality	503 (84)	120 (83)	126 (73)	311 (87)
Environmental exposures[a]				
Exposure to tobacco smoke (*N* = 498)	176 (29)	48 (34)	52 (32)	89 (26)
Comorbidities				
BMI *Z* Score (median, IQR; *N* = 505)	0.13 (−0.55–1.01)	0.13 (−0.51–0.97)	0.28 (−0.50–1.22)	0.10 (−0.58–0.91)
Eczema diagnosis (*N* = 460)	206 (37)	51 (39)	46 (31)	119 (38)
Hay fever diagnosis (*N* = 509)	273 (44)	64 (46)	59 (35)	163 (47)
Wheeze over time				
Preschool wheeze	340 (65)	91 (80)	88 (77)	187 (60)
Persistent wheeze	184 (36)	56 (49)	43 (38)	100 (32)
Asthma symptom control[a,b]				
≥1 wheeze attack (*N* = 502)	317 (63)	89 (79)	77 (70)	175 (63)
Wheeze affects activities (*N* = 505)	259 (51)	82 (74)	67 (61)	133 (43)
Any night wheeze (*N* = 502)	167 (32)	57 (51)	54 (49)	76 (25)
>5 days off-school (*N* = 512)	78 (15)	27 (24)	27 (24)	35 (11)
Dyspnoea (*N* = 502)	246 (49)	73 (66)	61 (55)	130 (43)
Severe wheeze (*N* = 503)	100 (20)	41 (37)	34 (31)	30 (13)
Other respiratory symptoms[a]				
Exercise-induced symptoms (*N* = 504)	339 (67)	87 (78)	72 (65)	198 (65)
Night cough (*N* = 501)	215 (43)	54 (50)	58 (53)	120 (39)
Wheeze triggers[a]				
Allergens	247 (48)	71 (62)	62 (54)	129 (41)
Infections	281 (54)	79 (69)	75 (66)	150 (48)
Exercise	272 (53)	84 (74)	67 (59)	141 (45)
Number of triggers (median, IQR)	2 (0–4)	3 (2–5)	2 (1–4)	1 (0–3)
Asthma attacks (unscheduled visits)[a]				
Paediatrician (*N* = 501)	243 (39)	61 (44)	102 (61)	106 (31)
Emergency department (*N* = 490)	127 (21)	36 (26)	62 (38)	45 (13)
Hospitalisations (*N* = 485)	88 (15)	27 (20)	48 (29)	29 (9)
Diagnostic tests at baseline				
Positive allergy test[c] (*N* = 354)	292 (70)	69 (71)	77 (71)	161 (69)
High FeNO[d] (*N* = 462)	258 (49)	63 (55)	57 (43)	147 (48)
FeNO ppb (median, IQR)[e] (*N* = 421)	22 (11–40)	23 (11–47)	16 (8–33)	21 (11–38)
FEV_1 *Z* score (median, IQR) (*N* = 461)	−0.54 (−1.4–0.2)	−0.65 (−1.28–0.08)	−0.44 (−1.37–0.27)	−0.52 (−1.42–0.19)
FEV_1/FVC *Z* score (median, IQR) (*N* = 461)	−0.72 (−1.57–0.21)	−0.66 (−1.67–0.28)	−0.67 (−1.47–0.29)	−0.71 (−1.54–0.18)
FEF25-75 *Z* score (median, IQR) (*N* = 343)	−1.10 (−1.83–0.33)	−1.16 (−1.90–0.27)	−1.05 (−1.81- -0.19)	−1.08 (−1.79–0.37
% FEV1 bronchodilator increase (median, IQR) (*N* = 325)	7.3 (2.5–14)	7.3 (−0.7–13)	9.0 (2.1–14)	7.12 (2.64–14.1)

(Continues)

TABLE 1 (Continued)

	All (N = 516)	Suboptimal asthma control last 4 weeks of follow-up (N = 114)	Asthma attack during 1 year follow-up (N = 114)	Good control & no asthma attack at follow-up (N = 313)
Bronchodilator reversibility[f] (N = 325)	105 (31)	19 (25)	21 (31)	66 (32)

Abbreviations: FEF25-75, forced mid-expiratory flow; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; IQR, Interquartile range; SD, standard deviation.

[a]In the last 12 months at baseline.

[b]Detailed answers by category can be found in Table S4.

[c]ositive Skin prick test or allergen specific IgE for any allergen.

[d]Definition of high FeNO depended on technique used and specified cut-offs for each centre: 10 ppb when using an offline method and 20 ppb when using an online method.

[e]Including only those that performed an online measurement of FeNO.

[f]Bronchodilator reversibility defined as an increase in FEV1 of 12% or 200 mL after the use of a short acting beta-agonist (SABA).

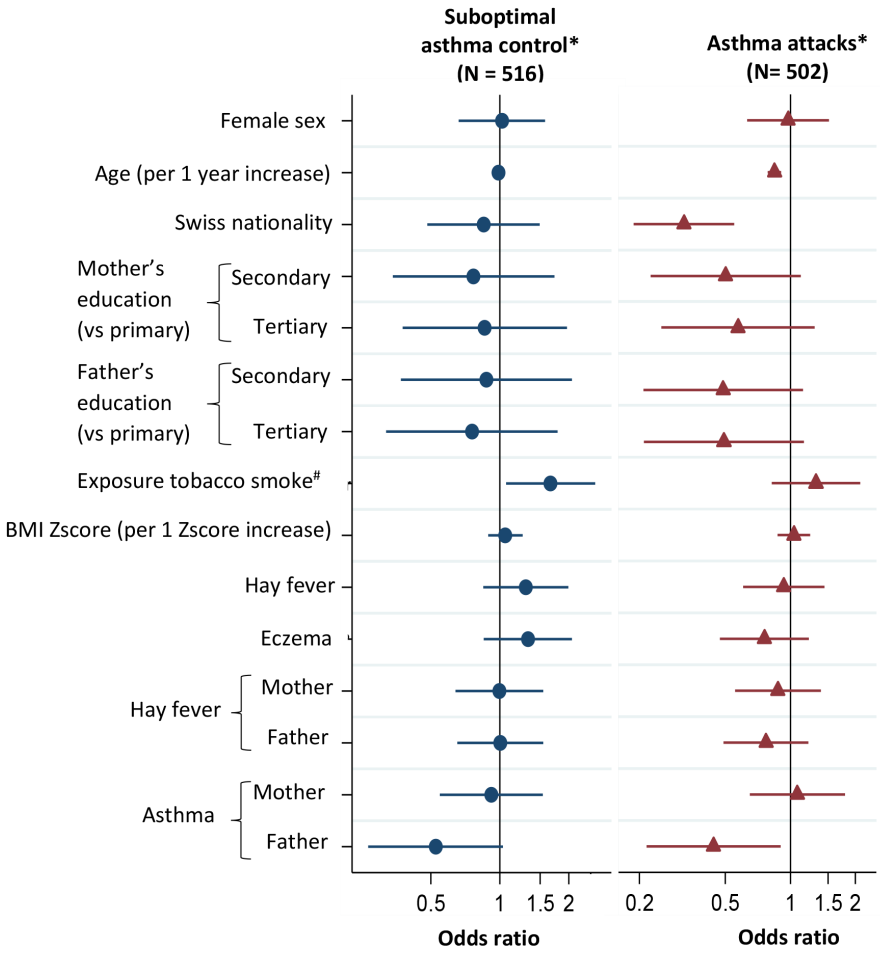


FIGURE 2 Personal and family factors and their association with suboptimal asthma control and asthma attacks 1 year later (Odds ratios based on logistic regression). *All variables were adjusted for age and sex. # Results for other environmental exposures are shown in Table S4.

None of the objective tests at baseline predicted suboptimal asthma control or asthma attacks at follow-up. There was only a slight association, between FeNO and suboptimal control (OR 1.07, 95% CI 0.99–1.16 per 10ppb increase). Baseline asthma therapy predicted suboptimal asthma control. Children on GINA Step 3 had a greater risk of having a suboptimal asthma control 1 year later compared to those on Step 1 (OR 2.38, 95% CI: 1.30–4.38), and a similar tendency, although not statistically significant, was seen for attacks (Table 1; Figure 4; Table S6).

4 | DISCUSSION

In this prospective study, we found that children at risk of poor asthma control are different to those at risk of asthma attacks. Only few (7%) were at risk for both. Suboptimal asthma control at follow-up was predicted by poor symptom control at baseline, wheeze triggered by allergens, colds and exercise, a more intense baseline treatment, history of preschool and persistent wheeze and exposure to tobacco smoke. Incident asthma attacks were predicted by

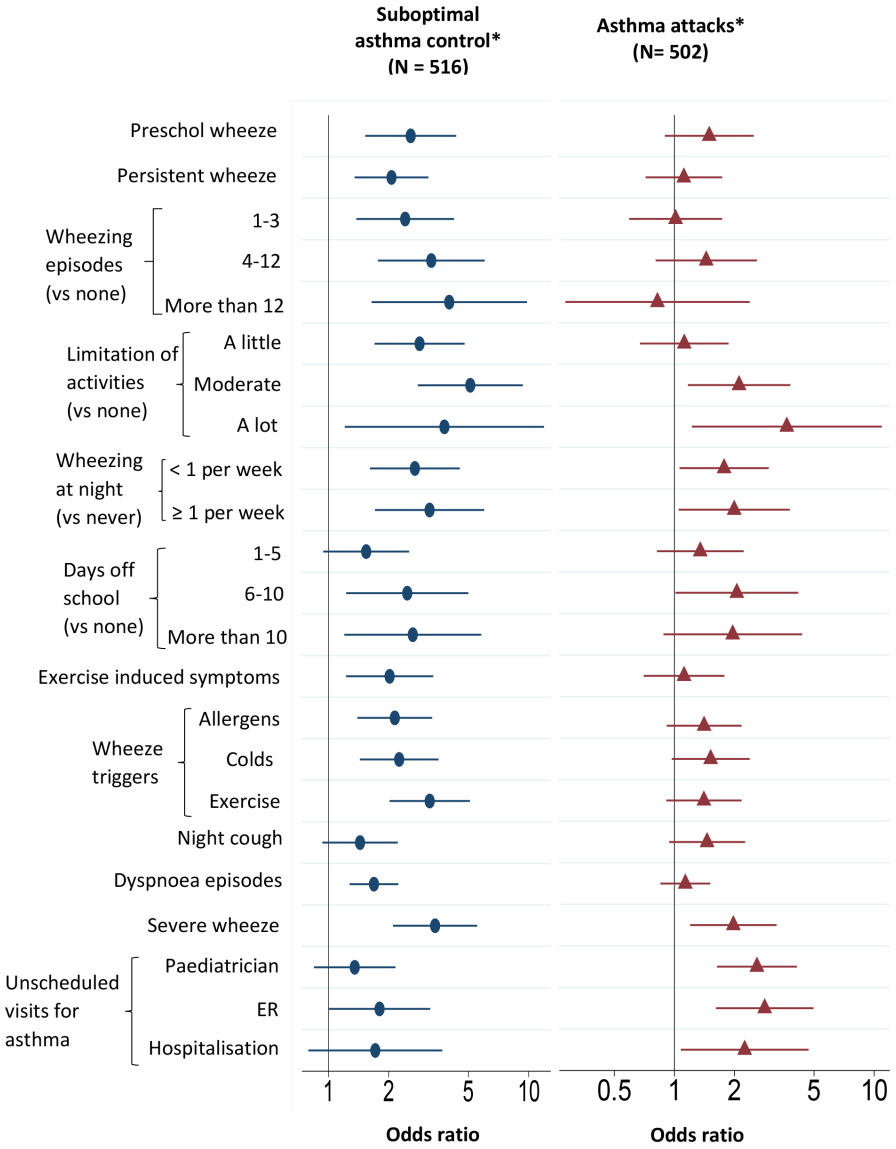


FIGURE 3 Respiratory symptoms and health care utilisation and their association with suboptimal asthma control and asthma attacks 1 year later (Odds ratios based on logistic regression). ER, emergency room. *All variables were adjusted for age and sex.

previous episodes of severe wheeze and previous asthma attacks at baseline, younger age, non-Swiss origin and no paternal asthma history. Lung function, FeNO and sensitisation at baseline were not associated with suboptimal control or asthma attacks 1 year later.

4.1 | Strengths and limitations

This longitudinal study embedded in routine care presents a unique opportunity to study asthma control and attacks in a real-life setting, which differs from highly controlled, selected populations of randomised controlled trials. The study findings are generalisable, as they come from a large multicentre study including most paediatric respiratory outpatient clinics in Switzerland. The prospective design allows to distinguish characteristics at baseline, from those observed at follow-up 1 year later, minimising measurement bias. We included a wide range of potential predictors, including a broad range of respiratory symptoms and objective tests. This study also has limitations. First, asthma attacks were parent-reported, potentially contributing to misclassification bias. However, asthma attacks that require unscheduled care are important events causing distress and are therefore normally well remembered within a 1 year period. Second, as the study is embedded in routine care, not all participants performed all the tests, as these depended on the treating physician. Third, we lacked information on treatment adherence, as this was not consistently nor objectively reported in the clinical visit health records. Finally, most children in this cohort had good long-term control of their symptoms and did not suffer an asthma attack during follow-up. Our findings may therefore not apply to children with more severe asthma or with unavailable or inadequate follow-up.

4.2 | Comparison with previous studies

Several studies have assessed factors associated with asthma control, though most are cross-sectional surveys. Predictors identified in these studies include ethnicity, parental unemployment, insufficient

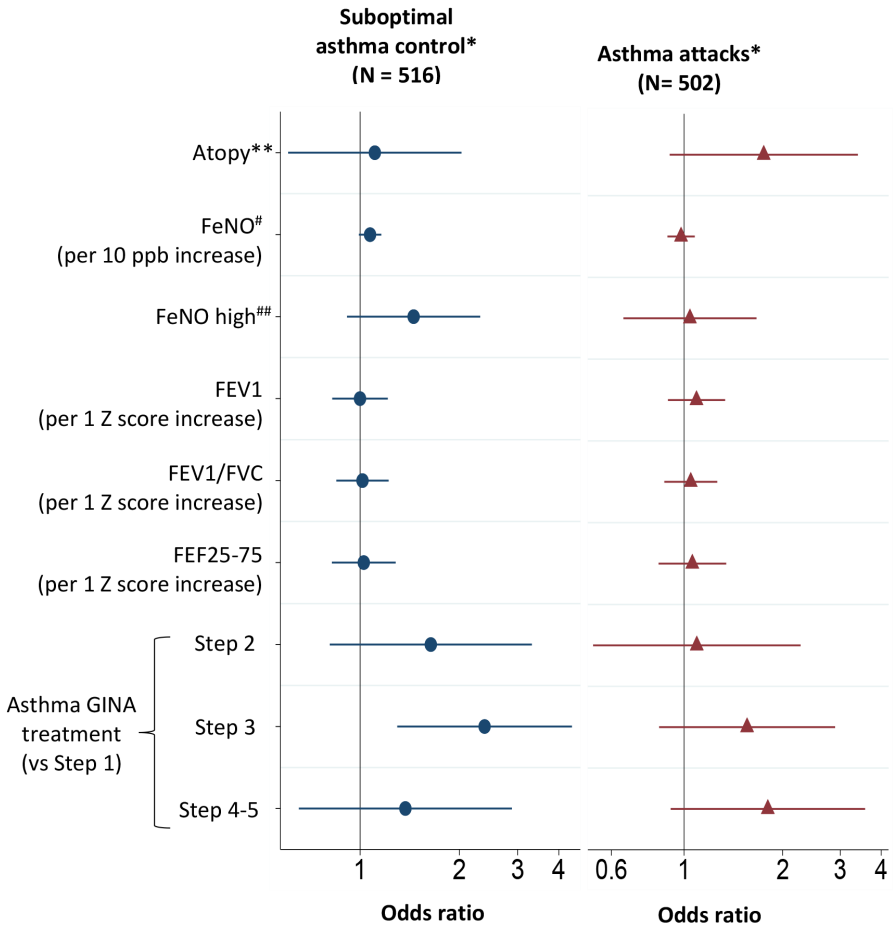


FIGURE 4 Objective test results and asthma treatment step, and their association with suboptimal asthma control and asthma attacks 1 year later (Odds ratios based on logistic regression). GINA, Global Initiative for Asthma; FEF 25%–75%: Forced mid-expiratory flow; FeNO, Fraction of exhaled nitric oxide; FEV1, Forced expiratory volume in the first second; FVC, Forced vital capacity. *All variables were adjusted for age and sex; ** Positive skin prick test or allergen specific IgE for any allergen; # Including only those that performed an online measurement of FeNO; ##: Definition of high FeNO depended on technique used and specified cut-offs for each centre: 10 ppb when using an offline method and 20 ppb when using an online method.

language comprehension, family history of asthma, recurrent respiratory infections, emotional distress, self-reported asthma severity, poor treatment adherence, no inhaled corticosteroid use, and history of asthma attacks.[3,5,18,19] Predictors of asthma attacks have been more extensively studied. These include younger age, African-American ethnicity, poverty, low parental education, inadequate health care access, poor symptom control, suboptimal drug regimen, comorbid atopic disease, obesity, vitamin D deficiency and tobacco smoke exposure. Previous asthma attacks were the strongest predictor.[17,20] However, we cannot compare predictors for these two outcomes if they have been assessed in different studies, because of variability in study populations, inclusion criteria, outcome definitions, and follow-up time. For instance, one study might have assessed predictors of asthma attacks within 12 months in 3–6-year-old children from the general population, while another study determined predictors of asthma control in 10–15 years olds visiting an allergy clinic, after an interval of 3 years. If results differed between these two studies, we would not know if the differences arose because the two outcomes differ (asthma attack vs. asthma control), or because of differences in the study population (age, prevalence of allergy, disease severity) or length of follow-up.

Our study found that predictors of long-term symptom control and asthma attacks differed. Even though baseline symptom control and attacks predicted both outcomes, symptom control at baseline was more consistently and more strongly associated with suboptimal asthma control at follow-up. This is shown by larger odds ratios for asthma control than for asthma attacks. Similarly, previous asthma attacks were more strongly associated (i.e. higher odds ratios) with incident asthma attacks than with future asthma control. Only two previous studies have analysed predictors for these two outcomes in the same setting. A post-hoc analysis of over 1000 children with mild to moderate asthma from the Childhood Asthma Management Program RCT[21] studied baseline factors associated with persistent (vs. intermittent) asthma symptoms and with asthma attacks. They found that persistent symptoms and attacks shared certain predictors, such as lower FEV_1/FVC ratio and bronchial hyperresponsiveness to methacholine. Younger age, prior asthma attacks and a higher eosinophil count predicted only asthma attacks. The second was a prospective observational study performed in British primary care, including 460 children with suspected or diagnosed asthma.[22] They found that poor symptom control and deprivation at baseline were associated with poor asthma control 6 months later, and that prior asthma attacks and a higher FeNO predicted attacks during follow-up. As ours, this study was embedded in routine care, but in a primary care setting. Additionally, children were only followed for 6 months and few children ($N = 175$) had information on symptom control at follow-up. Both studies, as ours, found that predictors for poor control and for attacks differed.

Both studies found an association between lung function or FeNO and asthma outcomes.[21,22] As our study, a recent meta-analysis of paediatric RCTs showed no association between

baseline FEV_1 and FeNO, and asthma control or attacks 3 months later.[34] It is important to note that in our study, paediatric pulmonologists already took test results into consideration when adjusting treatment, and this may help explain why objective tests did not predict symptom control or attacks in our setting. We had previously shown that lung function and asthma control were the main drivers for treatment step-up, while FeNO was the main driver for treatment step-down in SPAC.[35] However, in our current study, symptom control and previous asthma attacks were also considered by paediatric pulmonologists at baseline, and they still predicted future outcomes.

4.3 | Implications for practice and future research

We have shown that predictors for asthma control and asthma attacks differ, supporting the GINA guidelines' recommendations to assess these two dimensions of asthma control separately when adjusting medication in children.[1] We found that previous asthma symptom control and asthma attacks predicted future asthma outcomes in our study, unlike objective tests. More frequent follow-up and treatment adjustment of these children may improve their asthma control and reduce asthma attacks risk. In the meta-analysis of RCTs, a reduction in FEV_1 and an increase in FeNO 3 months after baseline evaluation predicted poor asthma control at 6 months, even though baseline values did not predict asthma outcomes at 3-month follow-up.[34] Only FEV_1 decrease 3 months after baseline evaluation predicted asthma attacks at 6 months. This suggests that 3-month follow-up visits with new FeNO and lung function measurements in children at risk of poor symptom control or asthma attacks may guide treatment adjustment to reduce the risk of poor asthma outcomes. Our result also suggests that we might need separate prediction scores to identify children at risk of poor symptom control and asthma attacks. Several prediction scores have been developed for asthma attack risk in children,[11–16] but most used retrospective or cross-sectional data, only one has been externally validated,[12] and none have been applied to clinical practice. No prediction score has been developed for asthma symptom control.

5 | CONCLUSION

We found that predictors of long-term suboptimal asthma control differ from those of attacks in children. Our results suggest that separate prediction scores for asthma control and attacks are needed to assess future risk of these individual treatable traits in children with asthma.

AUTHOR CONTRIBUTIONS

CEK and CAG conceptualised and designed the study. KH, AJ, AK, AM, NR, FS and CEK supervised data collection. ESLP, MCM, DO and CAG collected and prepared data. CAG analysed the data and drafted the manuscript. All authors critically revised the manuscript and read and approved the final manuscript as submitted.

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CONFLICT OF INTEREST STATEMENT

AM received consulting fees from Vertex Pharmaceuticals and Vifor Pharma; payments or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events received from Vertex Pharmaceuticals and Vifor Pharma; participation on a data safety monitoring or advisory board for Vertex Pharmaceuticals; and leadership or fiduciary roles in other boards, societies, committees or advocacy groups, paid or unpaid, held for European Respiratory Society Assembly 7, Swiss Society of Pulmonology board, Swiss Society of Pediatric Pulmonology board, Swiss Working Group for Cystic Fibrosis and Swiss Society for Sleep Research, Sleep Medicine and Chronobiology. Receipt of medical writing from Vertex Pharmaceuticals. All disclosures made outside the submitted work. FS received personal payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novartis Pharma Switzerland, Vertex Pharmaceuticals Switzerland, Vertex Pharmaceuticals Austria; and non-financial support from Chiesi Pharmaceuticals Austria outside the submitted work. The rest of the authors declare that they have no relevant competing interests.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkomission Bern 2016–02176) and the parents signed an informed consent form.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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