

Inhaled corticosteroids for recurrent respiratory symptoms in preschool children in general practice: Randomized controlled trial[☆]

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Abstract

Background: Therapy with inhaled corticosteroids (ICS) is beneficial in patients with asthma. However, in preschool children with symptoms like cough, wheeze, or shortness of breath diagnosing asthma is difficult. Therefore, the role of ICS in the management of preschool children with recurrent respiratory symptoms is unclear. We assessed the effectiveness of ICS in preschool children with recurrent respiratory symptoms in general practice.

Methods: In this multicenter, randomized, double blind, placebo controlled trial, 96 children aged 1–5 years consulting their general practitioners for recurrent respiratory symptoms and in whom treatment with ICS was considered by the general practitioner were randomly allocated to receive ICS (fluticasone propionate 200 mcg/day by metered dose inhaler/spacer combination) or placebo for 6 months. Outcome assessments were carried out 1, 3, and 6 months after randomization. The primary outcome measure was the symptom score (cough, shortness of breath and wheeze during day and night) as measured by a symptom diary card. Secondary endpoints were symptom-free days, use of rescue medication, adverse events, and lung function variables as measured by the interrupter technique and forced oscillation technique.

Results: During the 6 months treatment period, symptoms improved in both groups, with no differences between ICS and placebo. In addition, none of the secondary outcome parameters showed differences between both treatment groups.

Conclusion: ICS treatment has no beneficial effect in preschool children with recurrent respiratory symptoms in general practice. We therefore recommend a watchful waiting policy with only symptomatic treatment in these children. General practitioners and pediatricians should be aware of the high probability of overtreatment when prescribing ICS in these children.

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Keywords: Child; Preschool; Respiratory symptoms; Primary care; Anti-asthmatic agents; Inhaled corticosteroids; Efficacy of inhaled corticosteroids

Abbreviations: ICS, inhaled corticosteroids; FP, fluticasone propionate; GP, general practitioner; Rint, resistance by the interrupter technique; FOT, forced oscillation technique

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1. Introduction

For children under 5 years of age it is particularly difficult to distinguish between children with transient symptoms, i.e. viral wheeze, and those with persistent symptoms, i.e. asthma [1–3]. Currently, it is impossible to predict which infant with respiratory symptoms will develop asthma and which infant will not. Besides, it is also unclear which children with respiratory symptoms may require maintenance therapy for asthma [4,5]. At present, the decision to treat is not evidence based, which might result in undertreatment as well as overtreatment in these patients.

Inhaled corticosteroids (ICS) have become the cornerstone of maintenance therapy in patients with asthma [6]. The early introduction of ICS in childhood asthma is emphasized by current (international) guidelines [6–8]. However, particularly in preschool children, the benefits of ICS are less clear [9,10] and research in this area shows conflicting results [11–22]. ICS should only be prescribed in children who are likely to develop asthma in order to improve symptoms and lung function, reduce exacerbations and theoretically to prevent airway remodeling [5,23]. For children in whom respiratory symptoms are transient (about 2/3 of the total group with symptoms [1]) treatment with bronchodilators alone should be sufficient. Most studies evaluating the effectiveness of ICS in children have been carried out in populations of pediatric outpatient clinics. As a result, it is unknown whether ICS are effective in young children with recurrent respiratory symptoms presenting in primary care, where the majority of these children are treated. Furthermore, studies including lung function measurements in this age group have been rare to date [11,12,15,17,19,21,22]. Therefore, we designed a randomized controlled trial to assess the effectiveness of ICS in preschool children with recurrent respiratory symptoms in general practice using both subjective and objective outcome parameters; the ASTERISK (Asthma, Symptoms, Therapy, and RISK factors) study.

2. Methods

2.1. Recruitment

One hundred and eighty-two participating general practitioners (GPs) in the North of the Netherlands informed parents from children who presented with recurrent respiratory symptoms (cough, wheeze, and/or shortness of breath) in whom they considered to prescribe ICS for asthma (step 2 in the guidelines) about the ASTERISK study. Subjects were eligible if they were aged 1–5 years. GPs supplied the researcher with names and phone numbers of parents who were willing to participate. The researcher then contacted the parents to invite them for a screening visit at one of three research centers. Children who were treated with ICS

within 4 weeks prior to the study or oral steroids within 8 weeks prior to the study were excluded from the study. After the screening visit children entered a run-in period of two weeks in which parents recorded the respiratory symptoms of their child in a diary twice daily. During this period parents were also instructed to administer a placebo metered dose inhaler (pMDI) to the child by Babyhaler[®] twice daily in order to familiarize themselves with the use of the device. The persistence of the respiratory symptoms during this run-in period was the major inclusion criterion. Children with symptoms on less than 7 days or who used oral or inhaled steroids during the run-in period were excluded at the second visit (randomization visit). Other exclusion criteria were: other respiratory diseases, poorly controlled systemic diseases, inability of parents to fill in the study diary or to appropriately use the inhalation medication, and participation in other trials.

2.2. Study design

The ASTERISK study was a multicenter, double blind, randomized, placebo controlled trial. Children who fulfilled the eligibility criteria were randomly assigned to either the fluticasone propionate group (FP) or the placebo group. Randomization numbers were computer-generated in blocks of 4. All children received a numbered blinded metered dose inhaler which contained either FP or matching placebo. Consequently, the investigators as well as the parents were blinded.

For a period of 6 months children used 100 mcg (two puffs of 50 mcg FP or placebo) twice daily from a pMDI via a plastic spacer device (Babyhaler[®], GlaxoSmithKline, Zeist, The Netherlands) with face mask or mouth piece, according to the age and suitability of the device for each individual child. Throughout the study period participants were permitted to use salbutamol 200 mcg as required for symptom relief (rescue medication). Additional treatment during worsening of respiratory symptoms at the discretion of the GP was also permitted. Outcome assessments were carried out at 1, 3, and 6 months after randomization.

2.3. Symptom score

Our primary outcome variable was the symptom score assessed by diary record cards (DRC) as used in other studies [13,15,16]. Parents filled out the DRC twice daily during the run-in period and twice daily for 1 month prior to the visits at 1, 3, and 6 months. Parents rated their child's night-time and day-time symptoms (cough, wheeze, and shortness of breath) on a scale from 0 (no symptoms) to 3 (severe symptoms) each morning and evening. Thus, the total daily symptom score ranged from 0 to 18, and was averaged for each patient across the number of diary days during the run-in period and 1 month period prior to each of the three visits.

2.4. Symptom-free days/nights, rescue medication use, adverse events

Secondary outcomes were symptom-free days and nights, use of rescue medication and adverse events (AEs) (derived from the DRC).

2.5. Lung function measurements

In addition we measured lung function using two non-invasive techniques: the interrupter technique and the forced oscillation technique (FOT). Both methods require only passive co-operation and can be used in preschool children without sedation [24–26].

Interrupter technique: Using a commercial device (Micro-Rint[®], Micro Medical Limited, Rochester, Kent, England) according to the procedure as described in the literature [25] airway resistance (R_{int}) was estimated ($\text{kPa} \cdot \text{s} \cdot \text{L}^{-1}$). The interrupter technique has good repeatability [27,28] and is useful in preschool children when standardized procedures are followed [29].

FOT: Using a pseudo-random signaling (4–48 Hz) i2m[®] device (Chess, Antwerp, Belgium) according to a previously described method and guidelines [26,30], not only respiratory resistance (R_{rs} and R_{rs6} , $\text{hPa} \cdot \text{s} \cdot \text{L}^{-1}$) but also the reactance of the respiratory system (X_{rs} , $\text{hPa} \cdot \text{s} \cdot \text{L}^{-1}$) was assessed. Based on these data the frequency dependency over a frequency spectrum from 4 to 24 Hz, (f_{dep} , $\text{hPa} \cdot \text{s} \cdot \text{L}^{-1} \cdot \text{Hz}^{-1}$) and the resonance frequency, the frequency at which reactance is zero (f_{res} , Hz) were estimated. These parameters have been shown to correlate with airway narrowing [31].

2.6. Treatment adherence

We estimated adherence to treatment by determining the weight of the inhalers before and after the study ((the loss of weight of the inhaler as measured/the expected loss of weight of the inhaler)*100%). We considered a 70% of the expected loss weight as acceptable adherence.

2.7. Sample size

The sample size calculation was based on data from a previous placebo controlled trial with a treatment duration of 3 months in preschool children with recurrent asthmatic symptoms [16]. In this previous study, ICS resulted in a reduction of daily symptom score of 0.9 compared to placebo. The residual SD of the daily total symptom score was 1.4 with an upper 95% confidence limit equal to 1.5. It was calculated that with 66 patients in each group a mean difference in daily symptom score of 0.9 (= 0.60 SD-units) can be demonstrated with a power of 90% (two-sided alpha 0.05).

2.8. Statistical analysis

Differences between groups in the primary endpoint (mean symptom score) were estimated using linear mixed modeling

(SAS PROC MIXED). By applying the restricted maximum likelihood estimation method, missing values are taken into account in such a way that the estimated results satisfy the intention to treat principle. In the analyses we used the run-in score as a covariate. Lung function variables measured at each visit were analyzed similarly with adjustment made for height, weight, age and recent bronchodilator use as time dependent covariables, and as fixed covariables gender, smoking parents, smoking mother during pregnancy, and baseline lung function. The probability of a symptom-free day and night by visit and by treatment group during the treatment period was analyzed using generalized linear modeling (SAS PROC GENMOD) with a binomial distribution and a logit link function. The percentage of symptom-free days during run-in was taken as covariate in the analysis. Treatment effects (ICS vs. placebo) are expressed as odds ratios with 95% confidence intervals (CIs). The total number of rescue medications used by a patient was assumed to be proportional to the number of scoring days prior to each visit and analyzed using generalized linear modeling with a Poisson distribution and a log link function. Treatment effects (ICS vs. placebo) are expressed as rate ratios with 95% CIs. In the generalized linear models robust variance estimators were used in order to take the repeated measurements into account. The resulting estimated effects, however, do not satisfy the intention to treat principle. In case of a significant treatment-by-visit interaction ($p < 0.05$), effects are presented per visit; overall effects are presented otherwise. Effects on the lung function variables were estimated under condition of no recent bronchodilator used as effect-modifier in the model.

The percentage of patients who experienced AEs was compared between treatments using Fisher's exact test. The number of AEs was compared using the Mann–Whitney test. Initial patient characteristics (i.e. family history, age at onset, passive smoking, allergy markers, baseline lung function, etc.) were investigated for their possible modifying role of therapy effect on symptoms and lung function by incorporating the appropriate interaction terms in the linear mixed models.

2.9. Ethics

The study was approved by the Central Committee on Research involving Human subjects (CCMO) in The Netherlands as well as the local ethics committee in each participating center. Parents or guardians of all participating children gave their written informed consent for participation in this study.

3. Results

3.1. Study population

From June 2001 to January 2003 the 182 participating GPs enrolled 171 children. Of these 171 children, parents of 136 children agreed to participate and those children were seen accordingly for a screening visit before entering the run-in

period. Subsequently, 40 children did not meet the inclusion criteria and were excluded. Of these 40 children, 31 were excluded due to an insufficient number of days with symptoms during the run-in period. Finally, 96 children were randomly assigned to one of two treatment groups: fluticasone propionate for 6 months ($n = 48$) or placebo for 6 months ($n = 48$) (Fig. 1). During the treatment period eight children dropped out: three children due to worsening of symptoms (two in placebo group vs. one in FP group) and for the other five children due to non-compliance of the parents because of various reasons (three in placebo group vs. two in FP group).

The mean age of the included children was 2.6 years, two thirds (66) were boys. Baseline characteristics are shown in Table 1. There were no relevant differences between the two treatment groups.

3.2. Symptom score

Table 2 shows an improvement in total symptom score in both treatment groups with no statistically significant

differences between FP and placebo. The morning symptom score (night-time symptoms) as well as the evening symptom score (day-time symptoms) showed similar results.

3.3. Symptom-free days and nights (y/n) and rescue medication use

At 6 months of treatment, the percentage of symptom-free days increased comparably in the FP group and placebo group from 26% (95% CI 17–35%) to 62% (95% CI 52–71%) and 69% (95% CI 60–77%), respectively, with no differences between the two treatment groups. We found similar results for the percentage of symptom-free nights. This percentage increased from 41% (95% CI 31–50%) to 72% (95% CI 61–80%) after 6 months of treatment with FP and to 79% (95% CI 71–85%) after 6 months of treatment with placebo. No statistically significant differences on rescue medication use were found between both treatment groups (Table 3).

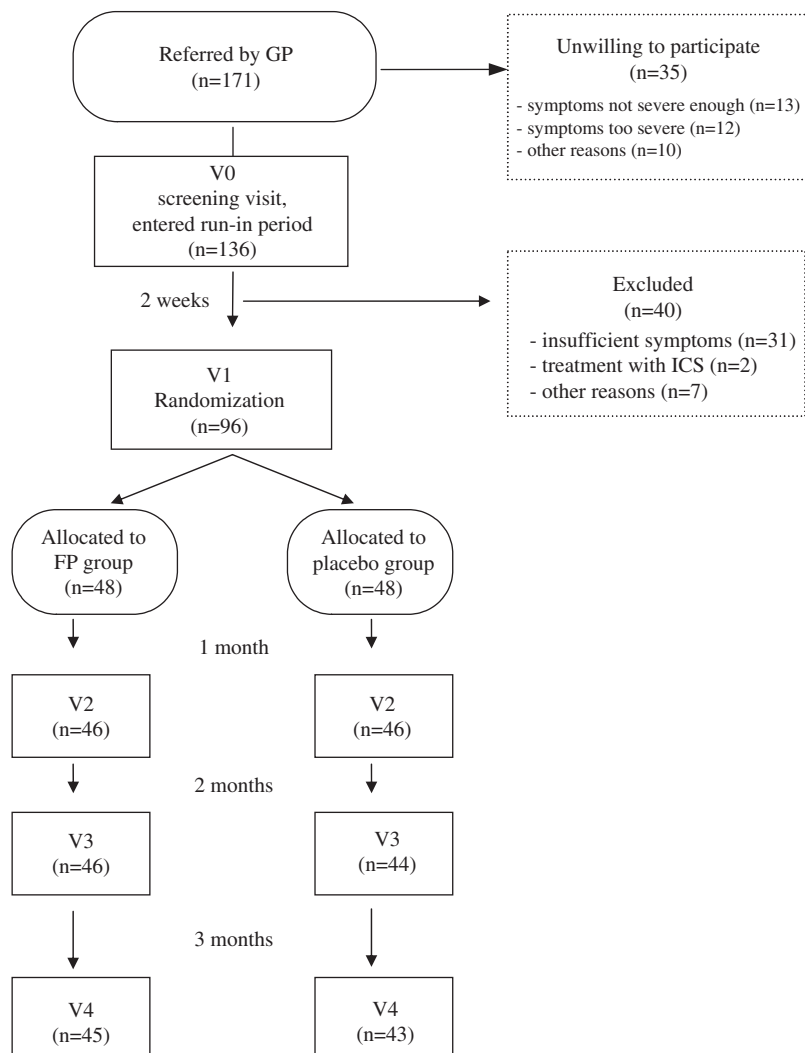


Fig. 1. Chart showing flow of children through the study.

Table 1
Baseline characteristics of children with recurrent respiratory symptoms by treatment group

	Fluticasone propionate group	Placebo group
<i>n</i>	48	48
Gender (male/female)	33/15	33/15
Age (years)	2.5 (1.2)	2.8 (1.2)
Height (cm)	93 (11); <i>n</i> = 45	95 (12); <i>n</i> = 47
Weight (kg)	14.5 (2.9); <i>n</i> = 45	15.1 (3.3); <i>n</i> = 47
Median (IQR) total IgE (U/ml)	33 (11–75); <i>n</i> = 47	29 (9–84); <i>n</i> = 46
Atopy (% positive phadiatop)	17; <i>n</i> = 47	22; <i>n</i> = 46
Eczema (%)	31	35
Median (range) age at onset (months)	6 (0–46)	8 (0–48)
Mother smoked during pregnancy (%)	26	21
Passive smoke exposure (%)	21	21
Use of salbutamol during run-in period (% yes)	81	77
Use of inhaled corticosteroids in past (% yes)	33	44
Median (IQR) total symptom score (0–18)	1.9 (1.1; 3.2)	2.7 (1.4; 3.7)
Median (IQR) % symptom-free days	27 (7–50)	15 (0–41)
Median (IQR) rescue medication 'use during day	0.21 (0–1.11)	0.37 (0.012–0.98)
Severity of symptoms (parent perceived)		
Mild (%)	9	2
Moderate (%)	66	72
Severe (%)	25	26

Values are presented as mean (SD) unless stated otherwise. Total symptom score (range 0–18; with higher score indicating worse symptoms), percentage of symptom-free and rescue medication use were calculated from the 14 days during the run-in period.

Table 2
Symptom scores (DRC) at baseline and at 1, 3, and 6 months

Baseline		After 1 month treatment	After 3 months treatment	After 6 months treatment	Overall treatment effect	
					FP vs. Pla	<i>p</i> -Value
<i>Total symptom score (0–18)</i>						
FP		1.78	1.40	1.37		
	2.74	(1.40–2.15)	(0.98–1.82)	(0.95–1.78)	–0.11	0.64
Pla	(2.34–3.15)	2.03	1.67	1.13	(–0.56–0.35)	
		(1.66–2.41)	(1.26–2.08)	(0.72–1.54)		
<i>Total day-time symptom score (0–9)</i>						
FP		0.97	0.77	0.75		
	1.55	(0.76–1.18)	(0.52–1.01)	(0.53–0.97)	–0.094	0.47
Pla	(1.33–1.77)	1.18	0.95	0.64	(–0.35–0.16)	
		(0.98–1.39)	(0.71–1.19)	(0.42–0.86)		
<i>Total night-time symptom score (0–9)</i>						
FP		0.81	0.62	0.60		
	1.20	(0.64–0.99)	(0.43–0.82)	(0.40–0.81)	–0.0072	0.95
Pla	(0.99–1.40)	0.86	0.72	0.49	(–0.22–0.21)	
		(0.69–1.04)	(0.52–0.91)	(0.29–0.69)		

Results are estimates obtained from linear mixed modeling. Values are presented as mean (95% CI) adjusted for baseline. Lower score indicates less symptoms. FP, fluticasone propionate group; Pla, placebo group.

3.4. Adverse events

Two children (both in the placebo group) were admitted to the hospital because of worsening of their respiratory symptoms (shortness of breath and coughing). The number of children experiencing AEs was similar in both groups, 30 and 29 in the FP and placebo group, respectively. The occurrence of the most frequent reported AEs, i.e. worsening of respiratory symptoms (28 children), upper respiratory tract

infection (24 children), and fever (20 children), did not differ between the two treatment groups (Table 4).

3.5. Lung function

Of the 96 children included in the ASTERISK study, 59% and 41% of the children were able to perform Rint and FOT measurements at all visits, respectively. The 57 children (24 in FP group vs. 33 in placebo group) with

Table 3

Symptom-free days/nights and rescue medication use at baseline and at 1, 3, and 6 months

	Baseline	After 1 month treatment	After 3 months treatment	After 6 months treatment	Overall treatment effect	
					OR (95% CI)	p-Value
% Symptom-free days (probability)						
FP		46	57	62		
	26	(38–55)	(48–66)	(52–71)	0.99	0.95
Pla	(17–35)	40	56	69	(0.64–1.53)	
		(33–49)	(47–65)	(60–77)		
% Symptom-free nights (probability)						
FP		56	70	72		
	41	(47–64)	(61–79)	(61–80)	0.95	0.80
Pla	(31–50)	56	66	79	(0.61–1.46)	
		(48–64)	(58–74)	(71–85)		
					RR (95% CI)	p-Value
Rescue medication use during day						
FP		0.44	0.37	0.37		
	0.72	(0.32–0.62)	(0.24–0.58)	(0.22–0.63)	0.77	0.16
Pla	(0.55–0.94)	0.53	0.56	0.31	(0.54–1.11)	
		(0.38–0.74)	(0.39–0.79)	(0.20–0.49)		
Rescue medication use during night*						
FP		0.10	0.066	0.11		
	0.15	(0.062–0.16)	(0.030–0.15)	(0.056–0.23)	1.16	0.67
Pla	(0.11–0.20)	0.080	0.11	0.056	(0.60–2.24)	
		(0.048–0.13)	(0.071–0.17)	(0.029–0.11)		
RR (95% CI)		1.24	0.59	2.01		
Per visit		(0.63–2.43)	(0.23–1.53)	(0.75–5.34)		
p-Value		p = 0.54	p = 0.28	p = 0.16		

Results are estimates obtained from generalized linear modeling. Values are presented as means (95% CI) adjusted for baseline. OR, odds ratio FP to pla; RR, rate ratio FP to Pla; *significant treatment-by-visit interaction ($p = 0.020$). FP, fluticasone propionate; Pla, placebo.

successful Rint measurements were younger (mean age 3.3 years) as compared to the 39 children (14 in FP group vs. 25 in placebo group) with successful FOT measurements (mean age 3.7 years). Baseline lung function values did not differ between the two treatment groups (Table 5).

Table 6 shows the lung function parameters in the two treatment groups during the 6 month study period. There were no significant differences in Rint values between FP and placebo. We found similar results with respect to FOT parameters; except for a trend towards a beneficial effect of FP ($p = 0.058$) on f_{dep} 4–24 Hz, no statistically significant differences were found between both treatment groups.

3.6. Adherence to treatment

Adherence data showed no significant differences between treatment groups. The mean adherence (medication used as percentage of the prescribed medication) was estimated at 82% (± 41) and 92% (± 33) in the FP group and placebo group, respectively.

3.7. Factors associated with effect of ICS

Except for total IgE value at baseline, no factors (such as family history, eczema, smoking mother during pregnancy,

lung function at baseline e.g.) were found which modified the effect of ICS.

4. Discussion

Treatment with ICS in preschool children with recurrent respiratory symptoms in general practice for 6 months had no beneficial effect as compared to placebo. Consistent with other studies we found a considerable spontaneous improvement in symptoms such as cough, wheeze, and shortness of breath. This may reflect the natural course of respiratory symptoms, as it is known that symptoms are likely to be transient in the majority of children. Moreover, the objective lung function data we collected in our study demonstrated similar results, implicating the ineffectiveness of ICS in this population. Overall, this study adds evidence against the early and abundant use of ICS in preschool children with recurrent respiratory symptoms in primary care.

ICS use in childhood asthma has been the focus of many studies performed in pediatric outpatient populations. Research in general practice is scarce although a previously performed pilot study in primary care also failed to demonstrate benefits of ICS in preschool children with symptoms suggestive of asthma [32]. Nevertheless, our

findings support a number of results generated in hospital-based studies [14,21] whilst simultaneously contradicting studies in which a beneficial effect of ICS has been demonstrated [13,15,16,20,22]. A study in young children

Table 4
(Serious) adverse events in both groups during treatment period

	FP	Pla
<i>Serious</i>		
Hospitalization due to worsening Respiratory symptoms	0 (0)	2 (2)
<i>Non serious adverse events</i>	75 (30)	64 (29)
Worsening respiratory symptoms	20 (14)	20 (14)
Upper respiratory tract infection	17 (11)	16 (13)
Fever	17 (13)	9 (7)
Otitis media	5 (4)	3 (3)
Varicella zoster	2 (2)	3 (1)
Rash	3 (3)	1 (1)
Fungal infection	3 (2)	0 (0)
Bacterial skin infection	2 (2)	1 (1)
Enteriobiasis	2 (1)	1 (1)
Worsening eczema	0 (0)	2 (2)
Allergic reaction to mosquito bite	0 (0)	2 (1)
Febrile convulsion	0 (0)	1 (1)
(suspension) Oral candidiasis	0 (0)	2 (1)
Conjunctivitis	1 (1)	1 (1)
Pain in legs	2 (1)	0 (0)
Diarrhea	0 (0)	1 (1)
Scarlet fever	1 (1)	0 (0)
Sleeping problems	0 (0)	1 (1)

Number of adverse events (number of children experiencing adverse events).

FP, fluticasone propionate; Pla, placebo.

Table 5
Characteristics of children able to perform lung function

	Rint (<i>n</i> = 57)		FOT (<i>n</i> = 39)	
	FP	Pla	FP	Pla
<i>n</i>	24	33	14	25
Gender (male/female)	15/9	24/9	8/6	19/6
Age (years)	3.1 (1.1)	3.4 (1.0)	3.7 (0.9)	3.7 (0.8)
Height (cms)	97.9 (9.5)	100.5 (10.1)	103.0 (7.7)	103.7 (7.6)
Weight (kg)	15.7 (2.9)	16.1 (3.2)	16.6 (2.9)	17.0 (2.7)
Atopy (% positive phadiatop)	29	26	36	29
Mother smoked during pregnancy (%)	35	18	39	20
Passive smoke exposure (%)	50	50	57	42
Eczema (%)	39	37	43	35
Rint (kPa · s · L ⁻¹)	1.25 (0.51)	1.24 (0.59)		
Rint (%pred)	128 (46)	129 (47)		
<i>R</i> _{rs} (hPa · s · L ⁻¹)			8.1 (1.7)	7.8 (1.8)
<i>R</i> _{rs6} Hz (hPa · s · L ⁻¹)			11.0 (3.4)	9.7 (2.8)
<i>X</i> _{rs} (hPa · s · L ⁻¹)			−0.66 (0.99)	−0.39 (0.99)
<i>f</i> _{res} (Hz)			30.2 (4.6)	28.3 (5.0)
<i>f</i> _{dep} 4–24 Hz (hPa · s · L ⁻¹ · Hz ⁻¹)			−0.19 (0.12)	−0.14 (0.093)

Values are presented as mean (SD) unless stated otherwise. Rint, resistance by the interrupter technique. Rint (%pred), Rint value expressed as percentage of predicted; equation based on data from Kooi et al. [41]. *R*_{rs}, resistance of the respiratory system by the forced oscillation technique. *R*_{rs6}, resistance of the respiratory system at 6 Hz by the forced oscillation technique. *X*_{rs}, reactance of the respiratory system by the forced oscillation technique. *f*_{res}, resonance frequency by the forced oscillation technique. *f*_{dep}, frequency dependency by the forced oscillation technique. FP, fluticasone propionate; Pla, placebo.

(1–3 years of age) with moderate to persistent asthmatic symptoms which confirmed the efficacy of ICS within a pediatric dose range (100–200 mcg daily) [13], is often cited in discussions about ICS use in children in favor of the use of ICS. However, the authors suggest that the treatment effect is probably driven by a subgroup of children responding to ICS treatment. A recent review describing the clinical efficacy and safety of ICS in asthma emphasizes that the effectiveness of ICS in young children and infants might differ between subgroups of children, however, in daily clinical practice these groups are still indistinguishable due to the diagnostic difficulty [33]. A Cochrane review of studies in children with viral-induced wheeze demonstrated no effect of ICS [14]. On the other hand, in children that were more likely to have asthma, ICS seems to be effective [18]. Consequently, the need to predict who will respond to treatment, and who will not, is cardinal.

Few studies have researched specific subgroups of young children with a wheezing phenotype by addressing factors predicting the success of treatment with ICS in order to better understand the role of ICS. ICS may have a more pronounced effect in children with frequent symptoms and children with a positive family history of asthma [16], which has also been reflected in a recent study in infants (6–24 months of age), including only children with a positive first degree family history for asthma or atopy, showing a beneficial effect of ICS [20]. Recently, evidence supporting the use of ICS for symptomatic control in a select group of children who are at high risk for asthma (i.e. positive asthma predictive index) was produced by the results of the PEAK trial [34,35]. Nevertheless, this study did not demonstrate a subsequent disease-modifying effect

Table 6
Lung function (Rint and FOT) at baseline and at 1, 3, and 6 months

	Baseline	After 1 month treatment	After 3 months treatment	After 6 months treatment	Overall treatment effect	
					FP vs. Pla	p-Value
Rint (kPa · s · L⁻¹)						
FP		1.13	1.14	1.20		
	1.24	(0.97–1.30)	(0.99–1.28)	(1.09–1.31)	0.08	0.20
Pla	(1.10–1.39)	1.13	1.10	1.07	(–0.04–0.20)	
		(0.99–1.27)	(0.99–1.21)	(0.98–1.16)		
R_{rs} (hPa · s · L⁻¹)						
FP		8.03	7.45	7.76		
	7.93	(7.45–8.60)	(6.61–8.29)	(6.73–8.78)	0.18	0.55
Pla	(7.37–8.48)	7.68	7.75	7.49	(–0.42–0.77)	
		(7.26–8.10)	(7.04–8.46)	(6.78–8.20)		
R_{rs6} (hPa · s · L⁻¹)						
FP		10.03	8.94	8.78		
	10.16	(9.04–11.01)	(7.56–10.32)	(7.11–10.44)	–0.21	0.64
Pla	(9.19–11.12)	9.74	9.77	9.49	(–1.14–0.72)	
		(9.04–10.44)	(8.61–10.93)	(8.35–10.63)		
X_{rs} (hPa · s · L⁻¹)						
FP		–0.48	–0.30	–0.34		
	–0.49	(–0.90 to –0.068)	(–0.67–0.062)	(–0.79–0.11)	–0.086	0.56
Pla	(–0.80 to –0.18)	–0.41	–0.34	–0.064	(–0.38–0.21)	
		(–0.71 to –0.10)	(–0.66 to –0.017)	(–0.37–0.24)		
f_{res} (Hz)						
FP		28.0	26.9	27.6		
	29.0	(26.2–29.7)	(24.9–28.8)	(25.2–30.0)	0.076	0.91
Pla	(27.5–30.5)	28.1	27.5	25.9	(–1.33–1.48)	
		(26.8–29.4)	(25.8–29.1)	(24.3–27.6)		
f_{dep} 4–24 Hz (hPa · s · L⁻¹ · Hz⁻¹)						
FP		–0.17	–0.11	–0.096		
	–0.16	(–0.23 to –0.10)	(–0.17 to –0.060)	(–0.17 to –0.024)	0.04	0.06
Pla	(–0.19 to –0.13)	–0.18	–0.16	–0.17	(–0.001–0.084)	
		(–0.22 to –0.13)	(–0.21 to –0.12)	(–0.22 to –0.12)		

Values are presented as mean (95% CI) adjusted for baseline. Rint, resistance by the interrupter technique. R_{rs}, resistance of the respiratory system by the forced oscillation technique. R_{rs6}, resistance of the respiratory system at 6 Hz by the forced oscillation technique. X_{rs}, reactance of the respiratory system by the forced oscillation technique. f_{res}, resonance frequency by the forced oscillation technique. f_{dep}, frequency dependency by the forced oscillation technique. FP, fluticasone propionate; Pla, placebo.

of ICS after discontinuation of treatment [34]. Similar results, that is improvement in symptoms but no effect on the natural history of asthma or wheeze until the age of 5 years, were found in the IFWIN study in which wheezy preschool children with one atopic parent were included [36]. A study including a more heterogeneous population, that is infants with a maternal history of asthma after only one episode of wheezing, showed neither short-term benefits of ICS nor effect on the progression of the disease [37]. In this study ICS were given intermittently (2-week courses) instead of regularly. Furthermore, the results of a study [21] in wheezy infants (4–24 months of age) not selected on family history are comparable to our findings, i.e. no beneficial effect of ICS and no effect modification.

Beneficial effects of ICS on lung function parameters were shown in preschool children who had recurrent or chronic asthmatic symptoms using a rather high dosage of ICS (i.e. 500 mcg FP daily) [19]. Although the beneficial effects were not found for subjective parameters, decreased lung function appeared to predispose to a beneficial effect of ICS. In our study baseline lung function was not related

to treatment response. The effect of ICS on lung function may be restricted to children with a positive skin prick test for aeroallergen, since in one study the positive effect of ICS was restricted to those sensitized to aeroallergens [17]. In our study, analyses based on sensitization to aeroallergens failed to predict the response to ICS. However, our findings indicate a possible role of total IgE in modifying the effect of ICS. This needs to be confirmed in future studies.

Overall, the therapeutic dilemma, i.e. which child should be treated as if he or she has asthma, is still a challenge for health care providers, both GPs and pediatricians, involved in pediatric respiratory medicine.

The lack of a beneficial effect of ICS in preschool children with recurrent symptoms in our study might be explained in several ways. The children included in our study were enrolled from general practices, whereas most other studies were performed in a pediatric outpatient setting the results of which might not be representative of the population in general practice. Milder symptoms in children enrolled in general practice as compared to more severe symptoms in children enrolled in hospital-based

studies are likely, and have to be stressed when interpreting the findings of our study. Moreover, it is possible that in our study there were more children with transient symptoms than in other studies. The dosage of ICS used in our study was comparable with the recommended dosage in pediatric patients [7–9]. Hence, we do not assume that our findings are due to the use of an inadequate dose ICS. Incorrect inhaler technique is another common explanation for ineffectiveness of inhalation medication [38]. In our study, however, the inhalation technique was optimized by supervision at each visit, minimizing the influence of inaccurate medication use. By including children throughout all seasons of the year and randomly allocating them to placebo or FP, the seasonal influence was equally distributed among both groups. Therefore, a seasonal effect is not likely to have masked the effectiveness of ICS in this study.

Selecting children from general practice as in our study enables us to clarify the effectiveness of ICS in a primary care setting. This is important because the majority of children present with respiratory symptoms to their GP, where treatment decisions are made. The 96 children included were enrolled by 70 different GPs supporting the generalizability of our results to the real life primary care setting.

To our knowledge this is the first randomized study conducted in a primary care population of children with recurrent respiratory symptoms in which subjective as well as objective parameters are used as outcome parameters.

Our selection procedure resulted in a primary care study population representing the real life situation. We realize that this could have led to an underrepresentation of the number of children with persistent asthma. However, we included only children with symptoms persisting during the run-in period in order to exclude as many children as possible with transient symptoms (e.g. common colds etc.). In addition, the willingness of parents of all children in spending time (visiting the research centre 5 times) and effort (filling in DRC daily for several months and administering medication twice daily) on the study, strengthens our concept of including a group of children who suffered substantially from respiratory symptoms. Finally, and most importantly, the reason to be included into this study was because maintenance therapy with ICS, and presumably a diagnosis of asthma, was recently considered by their GP. As it is still almost impossible to predict with any certainty which child is likely to go on to develop asthma, it is not possible to generalize the results of our study to the individual treatment decision for each child. We acknowledge that there are individual children who will benefit from ICS treatment.

We aimed to include 132 children but due to the time period allocated for the study we were only able to include 96 children. With 48 patients per treatment group, the power equals 79% under the given assumptions, our findings are unlikely to be explained by a lack of power.

It is known that recruiting adequate numbers of patients represents a major problem to the completion of rando-

mized clinical trials, in particular in primary care [39,40]. Several factors such as methods and strategy of recruitment are known to be related to the final enrolment number. Since we asked GPs to recruit patients during GP consultation, we assume that time pressure and forgetfulness may have reduced our recruitment rate. Other factors such as organizational characteristics, GPs motivation, involvement, and financial reimbursement may have determined recruitment by GPs.

More research is needed to disentangle the diagnostic difficulties in preschool children with respiratory symptoms, in order that we can more appropriately target treatment with ICS to the right children, i.e. children with persistent symptoms. The development of diagnostic tools for asthma in preschool children is fundamental and would be helpful in the clinical setting as well as for research purposes.

In conclusion, our study showed that treatment with ICS in preschool children with recurrent respiratory symptoms in general practice is not more beneficial than placebo. In order to prevent unnecessary prescribing of ICS we recommend a watchful waiting policy with only symptomatic treatment for these children. If ICS treatment is being prescribed, clinicians should be aware of the potential for spontaneous improvement in symptoms unrelated to ICS use. Since natural disease resolution is likely, these children should be closely monitored so that maintenance treatment can be stepped down or withdrawn.

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