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Spirometric changes in children with asthma exposed to environmental tobacco smoke and treated with inhaled corticosteroids

Promene spirometrijskih pokazatelja kod dece sa astmom koja su izložena duvanskom dimu i lečena inhalacionim kortikosteroidima

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Abstract

Background/Aim. Corticosteroids are the most frequently prescribed anti-inflammatory treatment in asthma. A purpose of this study was to compare the spirometric parameters as a response to inhaled fluticasone propionate (FP) treatment in children with asthma, exposed and nonexposed to environmental tobacco smoke (ETS). **Methods.** The study included 527 children aged between 1 and 16 years with persistent asthma divided into the groups of ETS exposed (ETSE, n = 337) and ETS free (ETSF, n = 190) children. Spirometry was performed before (1st set of results) and after 6 months of FP treatment (2nd set of results). Good lung function (GLF) was defined as forced expiratory volume in one second (FEV_1) ≥ 85%, and "poor lung function" (PLF) as FEV_1 < 85%. **Results.** Among the ETSE children, 208 had one smoking parent, 129 had two, 228 had smoking mothers and 238 smoking fathers. The ETSE children received a higher FP dose ($p < 0.0001$) which was increased with the increase of the number of smokers in the family. The ETSE children had significantly lower lung function both in the 1st and 2nd sets of tests compared to the ETSF children ($p < 0.05$). After the FP treatment, both groups improved all spirometric parameters ($p < 0.001$). In the 2nd set of the spirometric tests, the children of smoking mothers had lower spirometry values compared to the children of smoking fathers ($p < 0.05$). The proportion of the children improving from the PLF to GLF after 6 months of FP was much higher among the ETSF than the ETSE children ($p < 0.05$). **Conclusions.** The ETSE children had lower spirometric values before FP. After 6-months of the FP treatment children in both groups improved the spirometric values, but the improvement was higher in the ETSF children.

Key words:
asthma; child, preschool; child; adolescent; parents; smoking; tobacco smoke pollution; respiratory function tests; fluticasone; administration, inhalation.

Apstrakt

Uvod/Cilj. Kortikosteroidi predstavljaju najčešće primenjivanu anti-inflamatornu terapiju u astmi. Cilj ovog istraživanja je bio da se uporede spirometrijski pokazatelji kao odgovor na terapiju inhalacionim flutikazon propionatom (FP) kod dece sa astmom, koja su izložena i koja nisu izložena duvanskom dimu (*environmental tobacco smoke* – ETS). **Metode.** Ispitivanjem je obuhvaćeno 527 dece uzrasta od jedne do 16 godina sa perzistentnom astmom, koja su podeljena u dve gupe: grupa izložena (exposed – E) duvanskom dimu (ETSE, n = 337) i ETSF grupa – deca neizložena duvanskom dimu (*free* – F, n = 190). Spirometrija je urađena pre propisivanja FP (1. set rezultata) i nakon 6 meseci primene FP (2. set rezultata). Dobra plućna funkcija (*good lung function* – GLF) je definisana kao forsirani ekspirijumski volumen u prvoj sekundi (FEV_1) ≥ 85%, a loša plućna funkcija (*poor lung function* – PLF) kao FEV_1 < 85%. **Rezultati.** Među ETSE decom, 208 je imalo jednog roditelja pušača, 129 je imalo dva, 228 je imalo majku pušača, a 238 oca pušača. ETSE deci je propisana veća doza FP ($p < 0{,}0001$), koja se povećavala sa povećanjem broja pušača u porodici. ETSE deca su imala značajno lošiju plućnu funkciju i u prvom i u drugom setu testova u odnosu na ETSF decu ($p < 0{,}05$). Nakon lečenja sa FP, obe grupe su poboljšale sve spirometrijske pokazatelje ($p < 0{,}001$). U drugom setu spirometrijskih testova, deca majki pušača imala su niže

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vrednosti spirometrijskih pokazatelja u odnosu na decu čiji su očevi pušači ($p < 0,05$). Procenat dece čija se plućna funkcija poboljšala od PLF do GLF nakon 6 meseci primene FP je bio mnogo veći među ETSF decom nego među decom 2. grupe ETSE ($p < 0,05$). **Zaključak.** Parametri plućne funkcije izmereni pre propisivanja FP su lošiji kod dece izložene duvanskom dimu, nego kod dece koja nisu izložena. Nakon šestomesečne primene FP poboljšani su parametri plućne funkcije kod obe ispitivane grupe, ali znatno više kod dece koja nisu bila izložena duvanskom dimu.

Ključne reči:
astma; deca, predškolska; deca; adolescenti; roditelji; pušenje; zagađenje duvanskim dimom; respiratorna funkcija, testovi; flutikazon; inhalaciona primena.

Introduction

Asthma, as the most frequent chronic disease in children, could be triggered by infection, allergens, psychological and hormonal factors, physical exercise as well as by environmental irritants and contaminants such as tobacco. A retrospective analysis of the data from 192 countries, done by Oberg at al. [1], showed that as many as 40% of children were regularly exposed to secondhand smoke. The World Health Organization (WHO), California Environmental Protection Agency, and the US Surgeon General Report have presented evidence of a higher incidence of the acute lower respiratory infections and acute otitis media, more hospital admissions and earlier onset of asthma in the environmental tobacco smoke (ETS) exposed children [2–4]. Many studies have provided evidence that a fetal exposure to the chemical mediators secondarily released in response to tobacco and postnatal passive smoking present a risk factor of reduced lung function [5–10]. The prenatal and postnatal effects of secondhand smoke may vary among individuals depending on the individual genetic susceptibilities and gene-environment interactions.

Corticosteroids are the most effective anti-inflammatory therapy for asthma. Several studies in adult asthmatics and chronic obstructive pulmonary disease (COPD) patients provided evidence that chronic inflammation in the airways of smokers may be resistant to the anti-inflammatory effects of corticosteroids [11–15]. Studying children, Cohen et al. [16] found that the ETS exposure may attenuate the beneficial effect of inhaled corticosteroids (IC) among the children with asthma.

Therefore, we conducted a study in order to: 1) assess whether the children with persistent asthma exposed to the ETS had the lower values of the lung function tests compared to the nonexposed ones, 2) examine if there was a difference between exposure to smoking mother or smoking father or to both smoking parents and 3) compare the effect of the inhaled corticosteroid treatment with the fluticasone propionate (FP) on the lung function parameters in the ETS exposed and nonexposed children with asthma.

Methods

Study design

This cohort study was conducted at the Children's Hospital for Respiratory Diseases and Tuberculosis, Belgrade, Serbia, from June 2011 to June 2012. We screened 726 children (6–16 years old) with persistent asthma, with one or more asthma exacerbations treated in the emergency unit in the preceding 12 months, not receiving systemic or IC for at least two months. The diagnosis of asthma was established according to the Global Initiative for Asthma (GINA) recommendations [17]. The lung function testing was performed by means of spirometry (Pneumoscreen, Jaeger) and according to the protocol of the European Respiratory Society [18]. The subjects were suspended from the use of short-acting β2 adrenergic agents at least 6 hours before the test. The following parameters were measured: vital capacity (VC), forced volume vital Capacity (FVC), forced expiratory volume during the first second (FEV_1), FEV_1/VC, peak expiratory flow (PEF), mean expiratory flow at 75% (MEF_{75}), mean expiratory flow at 50% (MEF_{50}), mean expiratory flow at 25% (MEF_{25}) and mean expiratory flow at 25%–75% ($MEF_{25–75}$) [19]. Spirometry was performed at the beginning of the study (1st set of results) and after 6 months of the IC treatment (2st set of results). We classified the asthma severity according to the baseline value of the lung function parameters rather than according to the intensity and frequency of asthma symptoms [20]. According to the $FEV_1 < 85\%$ or $\geq 85\%$ of predicted values by age, sex, height and weight, we divided children into groups with the poor lung function (PLF) and good lung function (GLF). This cutoff point was chosen in order to define the group of asthmatic children with the lowest 5% lung function [5].

Smoke free families and families with smoking parents (mother or/and father) were included into the study. Children who were active smokers themselves or had additional chronic illness such as nephritic syndrome, diabetes, epilepsy, etc., were not included in the study.

A FP metered dose inhaler (MDI) was used in the daily dosage ranging from 50 to 1,000 mcg for 6 months. The clinicians prescribed the initial FP dose according to the asthma symptoms, lung function parameters and patients' age. They were blinded to the child's ETS exposure. The dose was maintained through the 6 months of the study. The children below the age of 12 were instructed to use the FP MDI through the volumatic chamber. No one was treated with the long-acting β2 adrenergic agents or anti-leukotriene agents. An allergy and asthma history was obtained at the first visit. According to the responses and parental personal statements, we divided children into two groups: children exposed to ETS at home (exposed cohort – ETSE) and ETS free children (control cohort – ETSF), and scheduled for the regular check-ups every 2 months. The skin prick test (SPT) was performed and the total serum IgE was taken to all children [21].

The study was approved by the institutional review board of the Children's Hospital for the Respiratory Diseases

and Tuberculosis, Belgrade, Serbia and informed consents were obtained from the patients and parents/caregivers.

Participants

Out of 726 children, we excluded 129 for not meeting the entry criteria.

The remaining 597 children were divided into the ETSE, n = 382 (64%) and the ETSF, n = 215 (36%) groups.

Additional 45 children were excluded from the ETSE group due to acute asthma exacerbation, lost contact, etc., leaving a sample of 337 children. We divided the ETSE children into the three subgroups: children of smoking mothers (n = 228), children of smoking fathers (N=238) and children of both smoking parents (n = 129).

From the ETSF group, 25 children were lost for reasons similar to the ETSE group, leaving the sample of 190 children (Figure 1, patients enrolment flow chart).

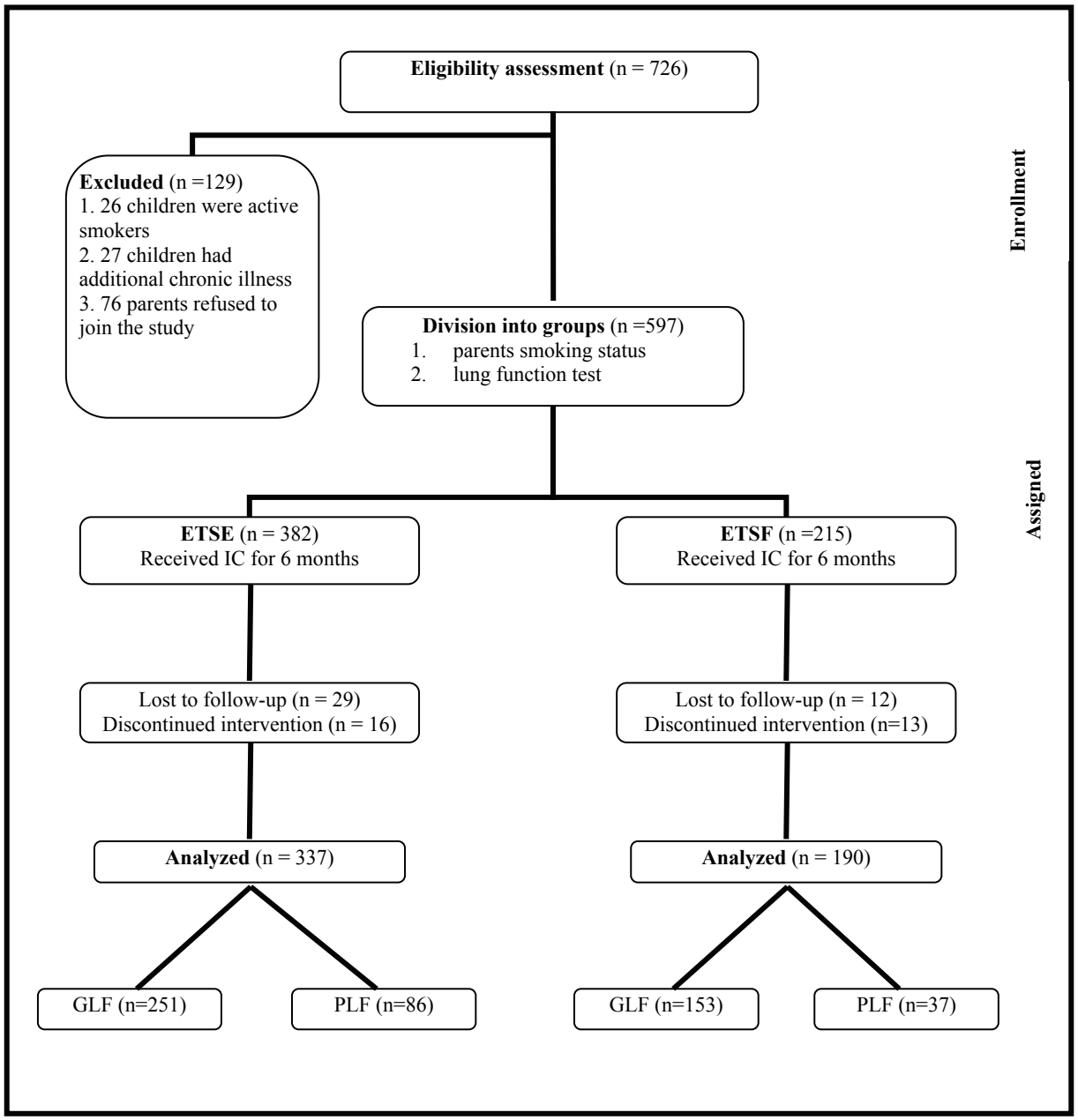

Fig. 1– Patients enrolment flow chart.
ETSE – environmental tobacco smoke (ETS) exposed children;
ETSF – environmental tobacco smoke (ETS) free children
GLF – good lung function – $FEV_1 \geq 85\%$ of predicted;
PLF – poor lung function – $FEV_1 < 85\%$ of predicted.

Statistical analysis

All data was statistically analyzed using the software SPSS 17 for Windows. The ordinal data was analyzed by the Pearson χ^2 test and the Fisher exact test if needed. The odds ratio (OR) with 95% confidence interval (CI) were calculated from 2*2 tables. The continuous variables are expressed as means ± SD. The numerical data (after verification of normal distribution by the Kolmogorov-Smirnov test) in two groups were compared with the Student *t*-test for related samples (since we had only 2 time points), and Fisher parametric ANOVA (Analysis of variance) for comparing more than two groups or more than two measures. Homogeneity of variance was checked for all variables and in all cases *p*-values exceeded 0.05. The Fishers Least Significant Difference (LSD) test was used for multiple comparisons. The results were controlled by the Tukey test that provided identical *p*-values in all instances. A probability value of $p < 0.05$ was considered statistically significant.

Results

In our sample of 527 children, there were 263 (49.9%) boys and 264 (50.1%) girls. There were 190 (36.1%) children with asthma living in the smoke free families, 208 (39.5%) living in the families with one smoking parent, and 129 (24.5%) living with two. There were 228 (43.3%) children living with actively smoking mothers (before the pregnancy 51% of mothers were smokers, during the pregnancy 41% continued to smoke) and 238 (45.2%) with actively smoking fathers.

In the first spirometry, the mean FEV_1 was 99.4% ± 16.4%. There were 432 (82%) children with asthma with $FEV_1 \geq 85\%$ of the predicted value.

There was no difference between the ETSF and ETSE groups according to sex, age, weight and height. However, the significant differences were recorded in the following baseline parameters: FEV_1 (101.9 vs. 98.2 respectively; $t = 2.47$, $p = 0.014$), total IgE values (320.9 vs. 603.6 IU/mL respectively; $t = 5.534$, $p < 0.0001$), at least one positive SPT (57.3% vs. 76.5%, $\chi^2 = 20.7$; $p < 0.0001$) and the number of asthma exacerbations in the preceding 12 months (5.3 ± 4.2 vs. 7.54 ± 10.7 respectively; $t = 2.75$, $p = 0.006$). The number of children, with $FEV_1 < 85\%$ of predicted, was significantly higher among smoking mothers ($\chi = 6.0$, $p < 0.05$), fathers ($\chi = 7.8$, $p < 0.05$) and both parents ($\chi = 7.6$, $p < 0.05$).

The arithmetic mean of the FP dose prescribed to all children was 225.1 ± 120.0 mcg per child per day. The ETSE received a significantly higher FP dose (Figure 2) than the ETSF children ($F = 31.2$, $p < 0.001$). There was no difference in the FP dose between the subgroups of the ETSE children.

According to the $FEV_1 \geq 85\%$ and $FEV_1 < 85\%$ of the predicted values and in the first spirometry and exposure to the ETS, we divided children into the subgroups: in the GLF group, there were 251 ETSE and 153 ETSF children, and in the PLF group there were 86 ETSE and 37 ETSF children. In the GLF group, the ETSE children had more exacerbations 12 months before the study, and a higher value of total IgE. They received a higher dose of the FP per day and had a higher percentage of at least one positive skin prick test compared to the ETSF children. In the PLF group, ETSE children had the higher value of total IgE and received a higher dose of FP compared to the ETSF children (Table 1).

All subgroups of the ETSE children had the significantly lower baseline values of all lung function test parameters than the ETSF children (Table 2).

In the final spirometry, the mean FEV_1 was 109.9 ± 14.2%. All ETSF and ETSE children significantly improved all lung function parameters 6 months after the introduction of the FP, except for the FEV1/FVC values in the children of smoking mothers ($p = 0.18$).

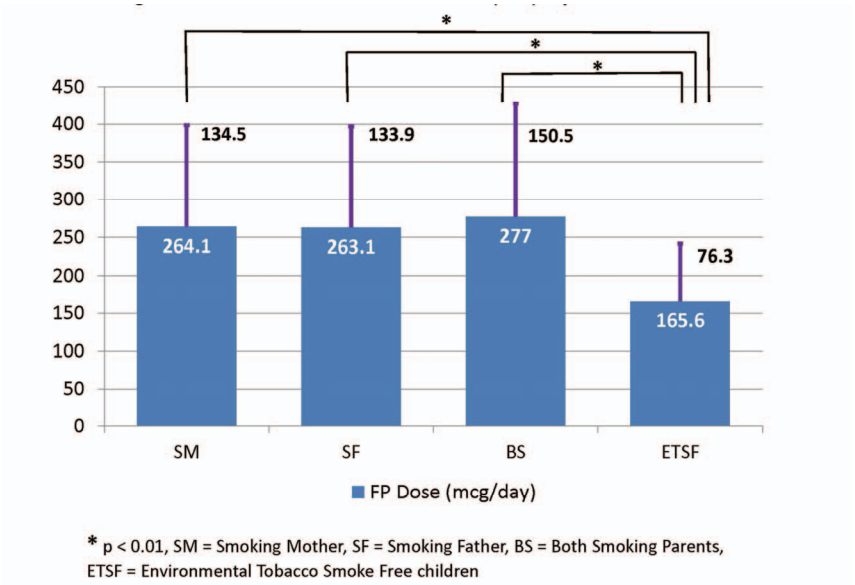

Fig. 2 – Mean values of daily dose of fluticasone propionate (FP) (mcg) according to the child's environmental tobacco smoke (ETS) exposition.

Table 1

Baseline characteristics of children with asthma

Characteristics	Good lung function*		Poor lung function†	
	ETSE (n = 251)	ETSF (n = 153)	ETSE (n = 86)	ETSF (n = 37)
Age (years), mean ± SD	10.0 ± 2.8	10.5 ± 2.9	10.6 ± 2.9	10.2 ± 2.8
Male sex (n, %)	141 (56.2)	85 (55.6)	42 (49.4)	17 (45.9)
Weight (kg), mean ± SD	43.7 ± 15.2	42.5 ± 15.9	34.4 ± 12.2	35.3 ± 11.6
Height (cm), mean ± SD	147.9 ± 17.5	147.6 ± 18.2	140.6 ± 16.9	139.0 ± 14.1
Numbers of exacerbations in last 12 months, mean ± SD	7.8 ± 12.1	5.1 ± 3.9	6.6 ± 5.6	6.9 ± 5.8
IgE (IU/mL), mean ± SD	641.9 ± 613.5	335.2 ± 6.9†	518.6 ± 569.0	271.9 ± 361.2†
FP (mcg)/ day, mean ± SD	246.8 ± 112.2	169.9 ± 85.4†	245.6 ± 130.0	158.8 ± 95.8†
SPT (n, %)	200 (79.7)	84 (54.9) †	66 (77.6)	27 (73)

ETSE – Environmental tobacco smoke (ETS) exposed children; ETSF – ETS free children; *Good lung function - $FEV_1 \geq 85\%$ pred; †Poor lung function – $FEV_1 < 85\%$ pred; SPT – Children with positive at least one skin prick test; *$p < 0.05$ and †$p < 0.01$ (Student's *t*-test or χ^2 test), as compared with the respective ETSE; SD – standard deviation.

Table 2

Lung function tests parameters between the children of non- smoking and smoking mothers, fathers, one and both parents, taken before (1st spirometry) and after 6 months (2nd spirometry) of the fluticasone propianate (FP) treatment

Parameter	Smoking	1st Spirometry			2nd Spirometry		
		mean ± SD	LSD	*p*	mean ± SD	LSD	*p*
FEV_1 (%pred)	ETSF	102.6 ± 15.4	ETSF–SM	< 0.001	108.9 ± 15.4	ETSF–SM	< 0.001
	SM	96.5 ± 15.7	ETSF–SF	< 0.001	102.9 ± 15.7	ETSF–SF	< 0.05
	SF	97.9 ± 17.1	ETSF–BS	< 0.001	105.8 ± 17.1	ETSF–BS	< 0.01
	BS	96.2 ± 15.6	SM–SF	> 0.05	104.4 ± 15.6	SM–SF	< 0.05
			SM–BS	> 0.05		SM–BS	> 0.05
			SF–BS	> 0.05		SF–BS	> 0.05
FEV_1/FVC (%pred)	ETSF	109.2 ± 9.4	ETSF–SM	< 0.001	110.5 ± 9.4	ETSF–SM	< 0.001
	SM	105.7 ± 11.5	ETSF–SF	< 0.05	106.5 ± 11.5	ETSF–SF	> 0.05
	SF	107.2 ± 10.5	ETSF–BS	< 0.01	109.1 ± 10.5	ETSF–BS	< 0.01
	BS	106.1 ± 11.9	SM–SF	> 0.05	107.7 ± 11.9	SM–SF	< 0.05
			SM–BS	> 0.05		SM–BS	> 0.05
			SF–BS	> 0.05		SF–BS	> 0.05
PEF (%pred)	ETSF	91.3 ± 17.0	ETSF–SM	< 0.001	96.7 ± 17.0	ETSF–SM	> 0.05
	SM	85.4 ± 16.7	ETSF–SF	< 0.01	94.7 ± 16.7	ETSF–SF	> 0.05
	SF	86.6 ± 17.5	ETSF–BS	< 0.001	97.9 ± 17.5	ETSF–BS	> 0.05
	BS	84.7 ± 16.2	SM–SF	> 0.05	97.7 ± 16.2	SM–SF	<0.05
			SM–BS	> 0.05		SM–BS	> 0.05
			SF–BS	> 0.05		SF–BS	> 0.05
MEF_{25} (%pred)	ETSF	93.8 ± 21.3	ETSF–SM	< 0.001	99.2 ± 11.3	ETSF–SM	< 0.001
	SM	82.2 ± 20.7	ETSF–SF	< 0.001	92.9 ± 10.7	ETSF–SF	> 0.05
	SF	85.5 ± 19.7	ETSF–BS	< 0.001	98.5 ± 13.7	ETSF–BS	> 0.05
	BS	83.0 ± 20.3	SM–SF	> 0.05	96.9 ± 10.3	SM–SF	< 0.01
			SM–BS	> 0.05		SM–BS	> 0.05
			SF–BS	> 0.05		SF–BS	> 0.05
MEF_{50} (%pred)	ETSF	94.0 ± 24.3	ETSF–SM	< 0.001	100.8 ± 14.3	ETSF–SM	< 0.001
	SM	80.7 ± 22.5	ETSF–SF	< 0.001	91.9 ± 12.5	ETSF–SF	< 0.05
	SF	84.0 ± 21.5	ETSF–BS	< 0.001	96.8 ± 11.5	ETSF–BS	< 0.01
	BS	81.2 ± 22.1	SM–SF	> 0.05	93.4 ± 12.1	SM–SF	< 0.05
			SM–BS	> 0.05		SM–BS	> 0.05
			SF–BS	> 0.05		SF–BS	> 0.05
MEF_{75} (%pred)	ETSF	94.9 ± 32.8	ETSF–SM	< 0.001	105.4 ± 12.8	ETSF–SM	< 0.001
	SM	80.5 ± 29.9	ETSF–SF	< 0.001	89.5 ± 19.9	ETSF–SF	< 0.05
	SF	81.7 ± 26.9	ETSF–BS	< 0.001	99.6 ± 16.9	ETSF–BS	< 0.01
	BS	81.0 ± 27.0	SM–SF	> 0.05	93.5 ± 17.0	SM–SF	< 0.01
			SM–BS	> 0.05		SM–BS	> 0.05
			SF–BS	> 0.05		SF–BS	> 0.05

ETSF – environmental tobacco smoke (ETS) free children (n = 190); SM – smoking mother (n = 228); SF – smoking father (n = 238); BS – both smoking parents (n = 129); LSD – Fisher's Least Significant Difference test for multiple comparisons; SD – standard deviation; FEV1 – forced expiratory volume during first second; FVC – forced expiratory volume; PEF – pear expiratory flow; MEF25 – mean expiratory flow at 25% of forced vital capacity; MEF50 – mean expiratory flow at 50% of forced vital capacity; MEF75 – mean expiratory flow at 75% of forced vital capacity.

The analysis of the 2nd set of spirometry results in Table 2 showed that: 1) the values of FEV_1, MEF_{50} and MEF_{75} were still lower in all subgroups of the ETSE children compared to the ETSF children; 2) the value of FEV_1/FVC was lower in the children of smoking mothers and both smoking parents compared to the ETSF children while there was no difference between the children of smoking fathers and the ETSF children; 3) the value of MEF_{25} was lower in the children of smoking mothers compared to the ETSF children, however, there was no difference in the children of smoking fathers and both smoking parents compared to the ETSF children; 4) the children of smoking mothers had lower values of all lung function test parameters compared to the children of smoking fathers; 5) there was no difference in PEF between the ETSE and ETSF children.

There was no difference in FVC between the ETSF and ETSE children both in the 1st and 2nd sets of tests.

The improvement in IC was quite similar between the ETS exposed and not exposed children except in a few points. In the children of non-smoking mothers, an improvement of MEF_{25} was significantly higher ($p < 0.05$) compared to the children of smoking mothers. The children of smoking fathers had a significantly better improvement in MEF_{75}, MEF_{50} and MEF_{25} ($p < 0.05$) compared to the children of non-smoking fathers. The children of both smoking parents had a significantly better improvement in PEF and MEF_{75} ($p < 0.05$) compared to the children of both non-smoking parents (Table 3).

The comparison of FEV_1 according to the ETS exposure in the GLF and PLF children before and after the FP treatment estimated the risk of having poor lung function (Table 4). The percentage of children improving from the PLF to GLF after 6 months of the FP treatment was much higher in the ETSF than in the ETSE children. In the ETSE group, 51% of children passed from the PLF to GLF group. In the ETSF group, 82% of children passed from the PLF to GLF.

Discussion

In this study a high percentage of smoking families (63.9%) was found, which is common in developing countries [22–25].

Baseline characteristics of the ETSE children showed that they had lower FEV_1, higher total IgE, more positive SPT and more previous asthma exacerbations compared to ETSF children. The ETSE children received a significantly higher FP dose per day. We assume that the clinicians prescribed higher doses of IC to the patients with more intensive symptoms and lower spirometry parameters, regardless of the child's tobacco exposure.

In this study, children with $FEV_1 < 85\%$ had more smoking parents [6]. In the GLF group, the ETSE children had more exacerbations 12 months before the study, had higher serum IgE values, received higher doses of FP per day, and had a higher percentage of at least one positive SPT compared to the ETSF children. In the PLF group, the ETSE children had higher the total IgE level and received a higher dose of FP per day compared to the ETSF children. Further analysis is required to determine whether the increased rate of exacerbations was linked with the IgE status and not the ETS status. Another question is whether the ETSE children additionally suffered from another respiratory problem (COPD type). Many studies confirmed that children exposed to tobacco smoke had more exacerbations which are red flags of poor control [1–4, 9, 10, 26]. Some studies have documented an association between maternal smoking during pregnancy and elevated cord blood total IgE as well as an increased risk for the development of some allergic disease [27, 28]. Other studies, however, did not replicate these findings. The updated meta-analysis of the evidence relating parental smoking to allergic sensitization in children as measured by SPT, the IgE levels, and presence of allergic rhinitis and eczema did not show any significant association of maternal smoking with the total serum IgE, allergic rhinitis, or eczema, and had no effect on secondhand smoke on skin-prick positivity [29, 30]. Farooqi and Hopkin [31] suggested that there was no significant association between maternal smoking and atopy, and maternal atopy constitutes the main risk for the development of atopy in children. This study was conducted in children with asthma, and a significant difference was shown in the total serum IgE and positive SPT between the ETSE and ETSF children.

As we expected, the lung function test parameters in the ETSE and ETSF children significantly improved on IC. However, the lung function parameters in the ETSE children never reached the values of those in the ETSF children. What we found interesting was that the children of smoking mothers had lower values of all lung function test parameters in the final spirometry compared to the children of smoking fathers. This was probably due to the amount of the time smoking mothers spend at home with children and consequently the higher ETS exposure. Our findings confirmed the findings of many other studies that reported differences in the lung function between the children with asthma exposed and nonexposed to the ETS [1, 6, 8]. An international study of parental smoking and lung function in more than 20,000 primary school children showed the lasting effect of smoking during pregnancy on the lung function, while the effects of past and current ETS exposure were smaller [5]. Other studies exploring the effects of ETS on asthma severity showed that the ETS exposed individuals had worse lung function, more exacerbations, more health care resource utilization, and a higher level of bronchial hyperreactivity in comparison to those who were not exposed [6–10].

The comparison the 1st and the 2nd set of spirometric results in the ETSF and ETSE children showed that some lung function parameters improved more in the ETSF and some in the ETSE children. Practically, the improvement was similar in both groups, although the ETSE children took higher doses of FP. This finding is in contrast with studies providing evidence that the ETS exposure may attenuate the beneficial effect of IC among children with asthma [16].

The proportion of children improving from the PLF to GLF after 6 months of FP was much higher among the ETSF children compared to the ETSE children. This is in accordance with the work of Cohen et al. [16] who found that fetal exposure to chemical mediators secondarily released in response to tobacco impaired the response to inhaled corticosteroid in children with asthma.

Table 3

Comparison of improvement between the 1st and 2nd spirometry in the children of non-smoking and smoking parents (mothers, fathers and both parents), (two-way ANOVA)

Parameter	Spirometry	Smoking	Smoking mother (n = 228)			Smoking father (n = 239)			Both smoking parents (n = 129)		
			Mean	SD	d*	Mean	SD	d*	Mean	SD	d*
FEV_1 (% pred)	1st	no	101.6	16.7	6.5	100.6	15.7	5.4	100.4	16.6	5.8
	2nd		108.1	13.2		106.0	14.5		106.2	14.2	
	1st	yes	96.5	15.7	6.4	98.0	17.2	7.7	96.4	15.7	8.3
	2nd		102.9	14.9		105.7	13.7		104.7	14.0	
FEV_1/VC (% pred)	1st	no	109.0	9.1	1.6	107.9	10.2	0.7	108.1	9.7	1.1
	2nd		110.6	7.8		108.6	9.1		109.2	8.7	
	1st	yes	105.7	11.5	0.8	107.2	10.5	1.9	106.1	11.9	1.7
	2nd		106.5	10.2		109.1	9.1		107.8	10.1	
PEF (% pred)	1st	no	90.4	17.7	6.8	89.6	17.3	5.0	89.3	17.6	6.2
	2nd		97.2	15.4		94.6	16.5		95.5	16.3	
	1st	yes	85.5	16.8	9.2	86.7	17.5	11.3	85.0	16.4	13.0*
	2nd		94.7	17.4		98.0	15.9		98.0	16.1	
MEF_{75} (% pred)	1st	no	91.9	20.5	7.5	89.5	22.1	5.6	89.2	21.2	7.2
	2nd		99.5	18.4		95.1	21.5		96.4	20.6	
	1st	yes	82.3	20.7	10.6	85.6	19.7	12.9*	83.2	20.5	14.1*
	2nd		92.9	22.4		98.5	19.0		97.3	20.3	
MEF_{50} (% pred)	1st	no	91.6	23.2	9.1	89.3	24.8	7.7	88.8	23.7	9.2
	2nd		100.7	18.7		97.0	21.4		98.0	20.7	
	1st	yes	80.8	22.6	11.2	84.1	21.6	12.7*	81.3	22.2	12.3
	2nd		92.0	24.7		96.8	22.5		93.6	25.0	
MEF_{25} (% pred)	1st	no	90.4	31.4	15.4*	89.7	33.8	8.3	87.7	32.2	12.7
	2nd		105.8	27.3		98.0	29.7		100.4	29.7	
	1st	yes	80.6	29.9	8.9	81.8	26.9	17.8*	81.2	27.0	12.6
	2nd		89.5	31.8		99.6	31.3		93.8	32.1	

d – difference between the 2nd and the 1st spirometry ; * Significant increase in lung function between children exposed to smoking or non-smoking parents ($p < 0.05$) ; SD – standard deviation; FEV_1 – forced expiratory volume during the first second; VC – vital capacity; PEF – peak expiratory flow; MEF_{75} – mean expiratory flow at 75%; MEF_{50} – mean expiratory flow at 50%; MEF_{25} – mean expiratory flow at 25%.

Table 4

Relative risk for a child with asthma to have poor lung function (PLF) before (1st spirometry) and after 6 months (2nd spirometry) of the fluticasone propionate (FP) treatment, if exposed to enviramental tobacco smoke (ETS)

Parameter		Good lung function (GLF)		Poor lung function (PLF)		OR (95% CI)	*p*
		ETSE	ETSF	ETSE	ETSF		
I Spirometry	FVC (%pred)	252 (74.7)	153 (80.5)	85 (25.3)	37 (19.5)	1.4 (0.9 to 2.2)	> 0.05
	FEV_1 (%pred)	264 (78.3)	168 (88.4)	73 (21.7)	22 (11.6)	2.1 (1.3 to 3.5)	< 0.01
	PEF (%pred)	244 (72.4)	159 (83.7)	93 (27.6)	31 (16.3)	2.0 (1.2 to 3.1)	< 0.01
	MEF_{25-75} (%pred)	215 (63.8)	153 (81.0)	122 (36.2)	37 (19.0)	2.4 (1.6 to 3.7)	< 0.001
II Spirometry	FVC (%pred)	302 (89.6)	186 (97.9)	35 (10.4)	4 (2.1)	5.4 (1.9 to 15.3)	< 0.001
	FEV_1 (%pred)	301 (89.3)	186 (97.9)	36 (10.7)	4 (2.1)	5.6 (1.9 to 15.9)	< 0.001
	PEF (%pred)	304 (90.2)	164 (86.3)	33 (9.8)	26 (13.7)	0.7 (0.4 to 1.2)	> 0.05
	MEF_{25-75} (%pred)	263 (78)	177 (93.2)	74 (22)	13 (6.8)	3.8 (2.1 to 7.1)	< 0.001

FVC – forced vital capacity; FEV1 – forced expiratory volume during the first second; PEF – peak expiratory flow; M EF25–75 – mean expiratory flow at 25, 50 and 75% of forced vital capacity; OR – odd ratio; CI – confidence interval; ETSE – ETS exposed children (n = 337); ETSF – ETS free children (n = 190); GLF – FEV1 ⩾ 85% pred; PLF – FEV1 < 85% pred.

It is very important to educate children with asthma and their parents about the negative effects of the ETS [32, 33]. The education may decrease the future ETS exposure of a child. In addition, the smoking habits of parents represent a risk factor associated with the initiation of smoking during adolescence among children [34–36]. Many governments have conducted tobacco control campaigns, however, the adequate implementation of these measures is essential [37].

The limitation of this study was the investigators' inability to check the real ETS exposure of the children in their home environment. Another limitation was our inability to check parents' active or passive smoking status and passive smoking status of children by measuring carbon monoxide in the exhaled air with Smokerlyzer. Moreover, we did not perform a bronchodilator test with short acting β_2-agonists after the 1st spirometry to asses reversibility of bronchoconstriction in the airways of the ETSF and ETSE children. We thought it would be helpful to asses the lack of reversibility in the ETSE children and would suggest a COPD-like component of their illness, but the majority of the children (82%) had FEV1 $\geq$ 85% of predicted and in most of them the positive BDT could not be obtained. Finally, we were not able to assess direct compliance with the IC therapy.

Conclusion

The ETSE children had lower values of the lung function tests both before and after the FP treatment. The ETSE children were treated with higher doses of FP than the ETSF children. After 6 months of the IC treatment, both the ETSE and ETSF children significantly improved all lung function test parameters. However, the ETSE children did not reach the spirometric values of the ETSF children, despite receiving the higher IC doses. The improvement of lung function test parameters under the IC treatment was practically the same in the ETSF and ETSE children, but the improvement in the children of smoking mothers was significantly lower than in the children of smoking fathers. The proportion of children improving from the PLF to GLF after 6 months of FP was much higher in the ETSF than in ETSE children.

This study did not provide enough evidence that the ETS exposure may attenuate the beneficial effect of IC on children with asthma, suggesting that timely protection of children with asthma from adverse effect of ETS makes sense, since there is no proof that their airways respond less to IC, which is the case in adult smokers with COPD and asthma.

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REFERENCES

1. *Oberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A.* Worldwide burden of disease from exposure to second-hand smoke: A retrospective analysis of data from 192 countries. Lancet 2011; 377(9760): 139–46.
2. *United States Public Health Service.* US Surgeon General report: The health consequences of involuntary exposure to tobacco smoke. Washington DC, USA: USPHS; 2006.
3. *California Protection Environmental Agency.* Proposed identification of environmental tobacco smoke as a toxic contaminant. Sacramento, CA, USA: California Protection Environmental Agency; 2005.
4. *United States Public Health Service.* US Surgeon General report World Health Organization: International consultation on environmental tobacco smoke (ETS) and child health: Consultation report. Geneva, Switzerland: WHO; 1999.
5. *Moshammer H, Hoek G, Luttmann-Gibson H, Neuberger MA, Antova T, Gehring U*, et al. Parental smoking and lung function in children: An international study. Am J Respir Crit Care Med 2006; 173(11): 1255–63.
6. *Comhair SA, Gaston BM, Ricci KS, Hammel J, Dweik RA, Teague WG,* et al. Detrimental effects of environmental tobacco smoke in relation to asthma severity. PLoS One 201; 6(5): e18574.
7. *Radic SD, Gvozdenovic BS, Pesic IM, Zivkovic ZM, Skodric-Trifunovic V.*Exposure to tobacco smoke among asthmatic children: parents' smoking habits and level of education. Int J Tuberc Lung Dis 2011; 15(2): 276–80, i.
8. *Gergen PJ.* Environmental tobacco smoke as a risk factor for respiratory disease in children. Respir Physiol 2001; 128(1): 39–46.
9. *Svanes C, Omenaas E, Jarvis D, Chinn S, Gulsvik A, Burney P.* Parental smoking in childhood and adult obstructive lung disease: Results from the European Community Respiratory Health Survey. Thorax 2004; 59(4): 295–302.
10. *European Respiratory Society, European Lung Foundation.* European lung white book. The first comprehensive survey on respiratory health in Europe. Sheffield, UK: ERSJ Ltd; 2003.
11. *Barnes PJ.* Corticosteroids: The drugs to beat. Eur J Pharmacol 2006; 533(1–3): 2–14.
12. *Barnes PJ.* Histone deacetylase-2 and airway disease. Ther Adv Respir Dis 2009; 3(5): 235–43.
13. *Marwick JA, Ito K, Adcock IM, Kirkham PA.* Oxidative stress and steroid resistance in asthma and COPD: Pharmacological manipulation of HDAC-2 as a therapeutic strategy. Expert Opin Ther Targets 2007; 11(6): 745–55.
14. *Barnes PJ, Ito K, Adcock IM.* Corticosteroid resistance in chronic obstructive pulmonary disease: Inactivation of histone deacetylase. Lancet 2004 ;363(9410): 731–3.
15. *O'Byrne PM, Lamm CJ, Busse WW, Tan WC, Pedersen S.* The effects of inhaled budesonide on lung function in smokers and nonsmokers with mild persistent asthma. Chest 2009; 136(6): 1514–20.
16. *Cohen RT, Raby BA, Van Steen K, Fuhlbrigge AL, Celedón JC, Rosner BA*, et al. In utero smoke exposure and impaired

response to inhaled corticosteroids in children with asthma. J Allergy Clin Immunol 2010; 126(3): 491–7.
17. *Global Initiative for Asthma, GINA*. Global Strategy for Asthma Management and Prevention. 2010. Available from: http://www.ginasthma.org/documents/5/documents_variants/35.
18. *Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R,* et al. General considerations for lung function testing. Eur Respir J 2005; 26(1): 153–61.
19. *Zapletal A, Paul T, Samánek M*. Significance of contemporary methods of lung function testing for the detection of airway obstruction in children and adolescents (author's transl). Z Erkr Atmungsorgane 1977; 149(3): 343–71. (German)
20. Proceedings of the ATS workshop on refractory asthma: Current understanding, recommendations, and unanswered questions. American Thoracic Society. Am J Respir. Crit Care Med 2000; 162(6): 2341–51.
21. *Heinzerling LM, Burbach GJ, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S*, et al. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. Allergy 2009; 64(10): 1498–506.
22. *Fagerström K*. The nicotine market: An attempt to estimate the nicotine intake from various sources and the total nicotine consumption in some countries. Nicotine Tob Res 2005; 7(3): 343–50.
23. *Janovski N, Pešić I, Janovski-Lutovac T, Vušović R, Danilović M, Basara Z*. Study on children smokers in Serbia. Eur Respir J 1996; 9(Suppl23): s93.
24. *World Health Organization*. Global Youth Tobacco Survey (GYTS). Geneva, Switzerland: WHO. 2008.
25. *Mackay J, Crofton J*. Tobacco and the developing world. Br Med Bull 1996; 52(1): 206–21.
26. *Radić S, Zivković Z, Erdeljan N, Cerović S, Jocić-Stojanović J*. Influence of environmental tobacco smoke on characteristics of childhood asthma. Srp Arh Celok Lek 2009; 137(3–4): 152–9. (Serbian)
27. *Bergmann RL, Schulz J, Günther S, Dudenhausen JW, Bergmann KE, Bauer CP,* et al. Determinants of cord-blood IgE concentrations in 6401 German neonates. Allergy 1995; 50(1): 65–71.
28. *Magnusson C*. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. J Allergy Clin Immunol 1986; 78(5 Pt 1): 898–904.
29. *Strachan DP, Cook DG*. Health effects of passive smoking .5. Parental smoking and allergic sensitisation in children. Thorax 1998; 53(2): 117–23.
30. *Strachan DP, Cook DG*. Health effects of passive smoking. 6. Parental smoking and childhood asthma: Longitudinal and case-control studies. Thorax 1998; 53(3): 204–12.
31. *Farooqi IS, Hopkin JM*. Early childhood infection and atopic disorder. Thorax 1998; 53(11): 927–32.
32. *Radić S, Zivković Z, Erdeljan N, Smiljanić S, Laković G*. Influence of smoking habit on respiratory function in young asthmatics: follow-up study from 16-30 years of age. Srp Arh Celok Lek 2006; 134 Suppl 2: 100–3. (Serbian)
33. *Zivković Z, Radić S, Cerović S, Vukasinović Z*. Asthma School Program in children and their parents. World J Pediatr 2008; 4(4): 267–73.
34. *Andersen RM, Leroux BG, Bricker JB, Rajan KB, Peterson AV*. Antismoking parenting practices are associated with reduced rates of adolescent smoking. Arch Pediatr Adolesc Med 2004; 158(4): 348–52.
35. *Jackson C, Dickinson D*. Can parents who smoke socialise their children against smoking? Results from the Smoke-free Kids intervention trial. Tob Control 2003; 12(1): 52–9.
36. *Milton B, Cook PA, Dugdill L, Porcellato L, Springett J, Woods SE*. Why do primary school children smoke? A longitudinal analysis of predictors of smoking uptake during pre-adolescence. Public Health 2004; 118(4): 247–55.
37. *Taylor AL, Bettcher DW*. WHO Framework Convention on Tobacco Control: A global "good" for public health. Bull World Health Organ 2000; 78(7): 920–9.

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