

Urinary eosinophilic protein X, atopy, and symptoms suggestive of allergic disease at 3 years of age

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Background: Urinary eosinophilic protein X (U-EPX) measurement is easy to perform in children. However, its use for prediction, diagnosis, and monitoring of asthma and atopy is unclear.

Objective: We sought to investigate the relationship between U-EPX and clinical phenotypes suggestive of allergic diseases.

Methods: U-EPX measurement (RIA), respiratory questionnaires, and skin testing were completed at age 3 years in 903 children followed prospectively from birth. Specific airway resistance was measured in 503 currently asymptomatic children by using whole-body plethysmography during tidal breathing.

Results: Nonatopic children with wheezing or eczema had slightly increased U-EPX levels compared with nonatopic asymptomatic children. U-EPX levels (geometric mean EPX/creatinine ratio) were as follows: nonatopic asymptomatic children ($n = 313$), 61.3 $\mu\text{g}/\text{mmol}$ (95% CI, 56.4-66.6 $\mu\text{g}/\text{mmol}$); nonatopic children with wheezing ($n = 148$), 71.2 $\mu\text{g}/\text{mmol}$ (95% CI, 63.2-80.1 $\mu\text{g}/\text{mmol}$); nonatopic children with eczema ($n = 90$), 65.7 $\mu\text{g}/\text{mmol}$ (95% CI, 56.7-76.2 $\mu\text{g}/\text{mmol}$); and nonatopic children with wheezing and eczema ($n = 86$), 79.7 $\mu\text{g}/\text{mmol}$ (95% CI, 67.4-94.3 $\mu\text{g}/\text{mmol}$). Children who had persistent atopy early in life had significantly higher U-EPX levels at age 3 years (nonatopic at 1 and 3 years [$n = 263$], 63.4 $\mu\text{g}/\text{mmol}$ [95% CI, 58.4-69.0 $\mu\text{g}/\text{mmol}$]; atopic at 1 but not 3 years [$n = 24$], 65.1 $\mu\text{g}/\text{mmol}$ [95% CI, 43.8-96.7 $\mu\text{g}/\text{mmol}$]; nonatopic at 1 year and atopic at 3 years [$n = 62$], 90.0 $\mu\text{g}/\text{mmol}$ [95% CI, 74.6-108.4 $\mu\text{g}/\text{mmol}$]; atopic at 1 and 3 years [$n = 35$], 111.5 $\mu\text{g}/\text{mmol}$ [95% CI, 89.2-139.3 $\mu\text{g}/\text{mmol}$]; $P < .002$). Atopy alone and with wheezing, eczema, or both was associated with significantly increased U-EPX levels ($P < .0001$). Wheezing appeared to be associated with higher U-EPX levels compared with eczema in both atopic and nonatopic children. The highest U-EPX level was found in atopic children with a history of wheezing and eczema ($P < .0001$). There was no relationship between U-EPX level and lung function.

Conclusion: U-EPX level reflects the presence of atopy and associated symptoms and might be useful for monitoring the progression of allergic disease. (*J Allergy Clin Immunol* 2003;112:702-8.)

Key words: Urinary eosinophilic protein X, asthma, atopy, cough, allergy

The role of eosinophilic markers in the diagnosis and monitoring of atopic disease is still unclear. Eosinophils play a role in the airway inflammation seen in asthma, as well as the inflammatory processes of atopic dermatitis.¹⁻³ Of the 4 basic eosinophil granule proteins, eosinophilic protein X (EPX) is the only one that can be accurately measured in the urine.⁴ It has been shown to correlate well with eosinophil activation and serum eosinophilic cationic protein levels.^{3,5} The easy availability of urinary EPX (U-EPX) makes it suitable for routine use in pediatric practice, especially in the infants and toddlers who cannot perform reliable lung function measurements and from whom it is difficult to obtain blood samples.² In this age group the differentiation of infantile wheezing and asthma, as well as chronic cough and cough-variant asthma, is still a considerable clinical challenge.

As part of the National Asthma Campaign Manchester Asthma and Allergy Study, we measured U-EPX levels in children at 3 years of age, aiming to investigate the relationship between U-EPX and clinical phenotypes suggestive of allergic diseases.

METHODS

Study population

The National Asthma Campaign Manchester Asthma and Allergy Study is a prospective cohort study described in detail elsewhere.^{6,7} Briefly, the subjects were recruited in utero (8th to 10th week of pregnancy) by screening parents in the antenatal clinic using skin testing and a questionnaire regarding allergic diseases. Children were identified as at high risk, medium risk, or low risk of allergic disease, according to parental skin prick test (SPT) responses and questionnaire data by using the following criteria: high risk, both parents have positive SPT responses; medium risk, one parent has a positive SPT response; and low risk, both parents have negative SPT responses with no parental history of atopic disease.

Study protocol

During the first 3 years of life, parents were asked to keep diary cards regarding their child's health. These included parentally reported symptoms, physician-diagnosed illnesses, and any treatments received. All participants were invited to attend a review clinic at age 3 (± 4 weeks from birthday). A standard respiratory questionnaire was administered by the interviewer, and children were skin prick tested (dust mite, cat, dog, mixed grasses, egg, milk;

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Abbreviations used

EPX: Eosinophilic protein X
GM: Geometric mean
ICS: Inhaled corticosteroid
SPT: Skin prick test
sR_{aw}: Specific airway resistance
U-EPX: Urinary eosinophilic protein X

Bayer Corp, Elkhart, Ind). Skin test responses were regarded as positive if the wheal produced was at least 3 mm greater than that elicited by the negative control. Total and specific serum IgE levels (milk, egg, mite, cat, and dog) were measured with the UniCAP assay (Pharmacia Diagnostics, Uppsala, Sweden). Sensitization was defined as a concentration of allergen-specific IgE of greater than 0.35 kU/L.

Lung function (specific airway resistance [sR_{aw}]) was measured with a constant-volume whole-body plethysmograph (Master Screen Body 4.3; Erich Jaeger GmbH, Würzburg, Germany), as previously described,⁶ by using a single-step procedure from the simultaneously measured changes of respiratory flow and plethysmographic pressure, omitting the measurement of total gas volume. sR_{aw} was calculated from the medians of 5 technically acceptable loops. Three measurements of effective sR_{aw} were performed, and the mean of these measurements was used in the analysis. Children were asymptomatic at the time of assessment of lung function.

Children in the high- and low-risk groups (n = 470) were also reviewed at 1 year of age.

U-EPX measurement

Urine was collected at the clinic visit or on the same day and was refrigerated until placed in aliquots and frozen (−20°C, frozen within 10 hours of collection). Samples were analyzed in duplicate for EPX by means of a specific RIA (Pharmacia Diagnostics AB) after dilution of samples 11 times in a phosphate buffer, pH 7.4, containing 0.15 mol/L NaCl, 1% BSA, 0.1% Tween-20, 10 mmol/L Na₂EDTA, and 0.2% N-cetyl-N,N,N-trimethylammonium bromide.^{8,9} The detection limit was less than 3 µg/L, and the coefficients of variation on the basis of 3 control samples analyzed in 4 replicates on 25 occasions were between 4.1% and 5.8% within assays and between 2.7% and 3.7% between assays. Mean recoveries after addition of 3 purified EPX concentrations to 3 normal urine samples were 96%, 103%, and 105% of expected value.

Because total volumes of urine produced were not known, urinary creatinine level was measured with the alkaline picrate method (Jaffé reaction; HiCo Creatinine; Boehringer Mannheim GmbH, Mannheim, Germany). The results are presented as the U-EPX/creatinine ratio (in micrograms per millimole).

Statistical analysis

Statistical analysis was performed by using SPSS 10.1 software. Data were normalized by using the log-e transformation. Independent *t* tests, χ^2 tests, Pearson correlations, and ANOVAs were performed. *P* values of less than .05 were accepted as significant. U-EPX/creatinine results are presented as geometric means (GMs) with 95% CIs of the mean unless otherwise indicated.

RESULTS

Urine for U-EPX measurement was collected from 903 children attending the 3-year clinical follow-up. Boys (n = 479) had significantly higher U-EPX values than girls (GM U-EPX/creatinine ratio: 78.4 µg/mmol [95% CI, 73.1-84.0 µg/mmol] vs 66.3 µg/mmol [95% CI,

61.8-71.2]; *P* = .001). This could be related to the higher prevalence of atopy and symptoms among boys in this age group. However, even among healthy (no parentally reported symptoms suggestive of atopic disease) nonatopic children (n = 308), boys (n = 138) had significantly higher U-EPX levels than girls (GM and 95% CI: 68.9 µg/mmol [95% CI, 60.1-78.9 µg/mmol] vs 54.0 µg/mmol [95% CI, 48.8-59.7 µg/mmol]; *P* = .004).

Family and personal medical history and exposure to pets

Parental history of allergic disease, medical history other than atopic conditions in the child, and routine vaccinations (diphtheria, tetanus, pertussis, meningococcus C, *Haemophilus influenzae*, oral polio vaccine, and BCG) were not associated with U-EPX. Paternal but not maternal smoking was significantly associated with increased U-EPX levels (father smoker: 81.8 µg/mmol [95% CI, 74.1–90.4 µg/mmol] vs father nonsmoker: 69.6 µg/mmol [95% CI, 65.8-73.8 µg/mmol]; *P* = .006). U-EPX levels were significantly lower in firstborn children compared with levels in those with older siblings (66.2 µg/mmol [95% CI, 61.7-71.0 µg/mmol] vs 78.0 µg/mmol [95% CI, 72.7-83.6 µg/mmol]; *P* = .01).

Pet ownership (cat or dog) either at birth or at age 3 did not affect U-EPX measurement.

Atopy

At age 3 years, 819 of 903 children were skin prick tested, and of those, 181 (22.1%) were sensitized. Atopic children (≥ 1 positive skin test responses) had significantly higher U-EPX levels compared with those of nonatopic children (96.58 µg/mmol [95% CI, 86.6-107.7 µg/mmol] vs 66.3 µg/mmol [95% CI, 62.6-70.3 µg/mmol]; *P* < .001). We analyzed the individual allergens and their effects on U-EPX levels. This was compared with serum IgE results where available (Table I). Positive SPT responses for mold, milk, and egg were associated with the highest mean U-EPX values. However, overall numbers were small and do not permit a firm conclusion on the association. The association of positive SPT responses with increased U-EPX levels was confirmed by the serum IgE values, but numbers overall were lower (Table I).

There was a weak correlation between the number of allergens a child was sensitized to and the level of U-EPX ($r^2 = 0.21$, *P* < .001). Total serum IgE showed a significant positive correlation with U-EPX levels ($r^2 = 0.42$, *P* < .001).

At age 1 year, 423 of 470 children (medium-risk group not reviewed at age 1 year) underwent skin prick testing, and 62 (14.7%) of 423 were atopic. U-EPX was significantly higher in children with early persistent atopy (ie, both at 1 and 3 years) compared with other groups (nonatopic at 1 and 3 years [n = 263], 63.5 µg/mmol [95% CI, 58.4-69.0 µg/mmol]; atopic at 1 year but not at 3 years [n = 24], 65.1 µg/mmol [95% CI, 43.8-96.7 µg/mmol]; nonatopic at 1 year and atopic at 3 years [n = 62], 90.0 µg/mmol [95% CI, 74.6-108.4 µg/mmol]; and

TABLE I. Sensitization to various allergens and the associated increases seen in U-EPX levels

Allergen	SPT (≥3 mm)	n	U-EPX/creatinine ratio (μg/mmol)		P value	Specific IgE RAST ≥1	n	U-EPX/creatinine ratio, GM (μg/mmol)	P value
			GM	95% CI					
Dust mite	+	101	106.48	92.14-123.07	<.001	+	34	110.34	<.001
	—	747	68.36	64.77-72.16		—	187	66.82	
Dog	+	55	104.39	86.52-125.96	<.001	+	20	112.79	.005
	—	795	70.17	66.14-74.14		—	222	69.03	
Cat	+	53	100.34	84.59-119.02	.001	+	23	117.27	.001
	—	794	70.39	66.73-74.25		—	198	68.20	
Egg	+	34	110.12	85.52-141.80	.001	+	19	92.82	NS
	—	791	70.69	66.97-74.64		—	202	70.46	
Milk	+	5	134.67	69.52-260.84	.065*	+	14	116.31	.014
	—	818	71.69	68.04-75.71		—	207	69.87	
Mixed molds	+	3	233.69	121.39-449.93	.007	NA	—	—	—
	—	792	71.74	68.02-75.66					
Pollen	+	85	86.21	74.49-99.86	.02	NA	—	—	—
	—	764	70.44	66.71-74.39					

NS, Not significant; NA, not applicable.

atopic at 1 and 3 years [n = 35], 111.5 μg/mmol [95% CI, 89.2-139.3 μg/mmol]; *P* < .002).

Symptoms suggestive of atopic disease

The incidence of reported symptoms and their association with U-EPX is shown in Table II. Atopic dermatitis was significantly associated with increased U-EPX levels, with the highest levels seen when eczema was present on physical examination (Table II). Allergic rhinitis was not significantly associated with increased U-EPX, but the number of patients with allergic rhinitis was small (35 of 903). Physician-diagnosed asthma was strongly associated with increased U-EPX levels, with the highest levels found in children receiving asthma medication (Table II). Symptoms associated with the highest U-EPX levels were cough and wheezing on exposure to cold air (Table II).

Children receiving short-acting β-agonists (91 of 903 [10.1%]) had significantly higher U-EPX levels compared with those who did not (93.1 μg/mmol [95% CI, 79.5-109.0 μg/mmol] vs 70.5 μg/mmol [95% CI, 67.0-74.3 μg/mmol]; *P* = .001). There was a trend for the children receiving regular inhaled corticosteroids (ICSs) to have higher U-EPX values, but this failed to reach statistical significance (receiving ICS [n = 39], 88.5 μg/mmol [95% CI, 68.1-114.8 μg/mmol]; not receiving ICS [n = 839], 71.9 μg/mmol [95% CI, 68.2-75.7 μg/mmol]; *P* = .10).

Parentally reported wheezing and cough were both significantly associated with increased U-EPX levels. When children who had wheezed were excluded from analysis, the number of children with cough was smaller, and only “cough on exposure to cold air” remained significant (*P* = .05). When children with cough were excluded from the analysis, the associations of U-EPX and wheezing or a diagnosis and treatment of asthma were no longer significant, but the numbers for some of the groups were small. Fig 1 shows the combined effect of cough and wheezing on U-EPX values.

U-EPX levels appeared to increase with the increase in

parentally reported symptoms both in atopic and nonatopic children (wheezing and eczema > wheezing > eczema > no reported symptoms, Fig 2). However, atopic children had significantly increased U-EPX levels, and the values increased with increasing clinical disease (Fig 2).

Lung function

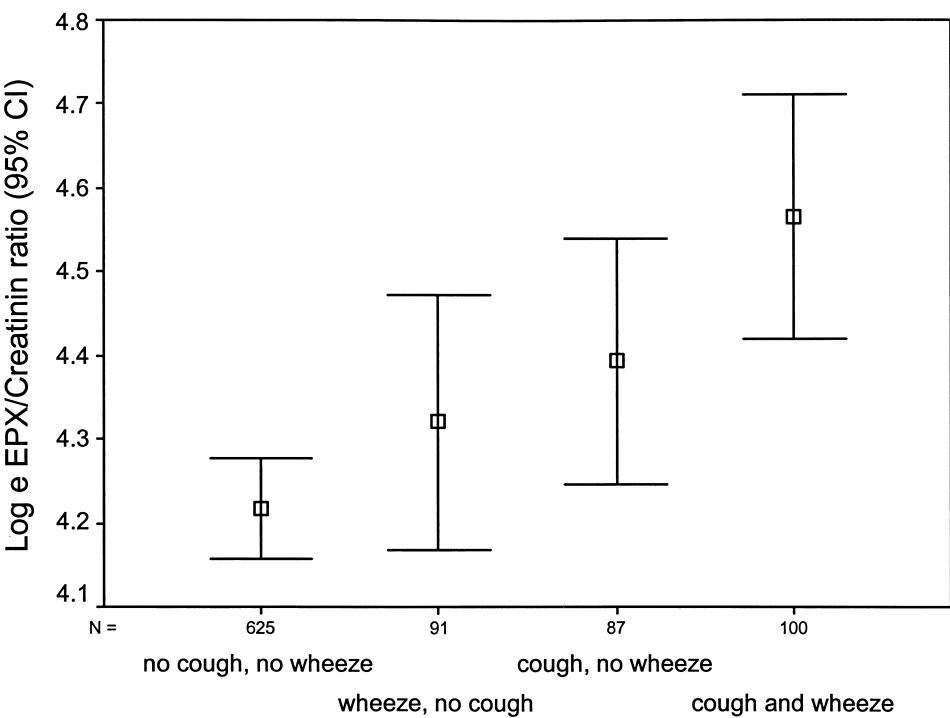
There was no significant correlation between U-EPX and sR_{aw} levels. sR_{aw} of greater than 1.3 kPa/s appears to be associated more commonly with symptoms of asthma. No significant difference between U-EPX levels of children with an sR_{aw} of 1.3 kPa/s or less and an sR_{aw} of greater than 1.3 kPa/s was found.

Multivariate analysis

A general ANOVA was performed, including variables found to be significant in the univariate analysis and those known to be associated with increased U-EPX levels from the literature. Independent significant associations with U-EPX levels were seen for atopy, wheezing (recent or ever), cough (more than others and on exposure to cold air), older siblings, sex, and eczema (present at physical examination; Table III). When more than 3 variables were included in the model, the associations of eczema and wheezing with U-EPX tended to lose their significance (Table III). Atopy was always significantly and independently associated, regardless of the number (up to 7) or nature of other variables included in the model. Significant interactions were seen for atopy and older siblings (both contributing to increasing the U-EPX value); atopy, older siblings, and cough; atopy and eczema; and atopy, eczema, and cough on exposure to cold air (Table III).

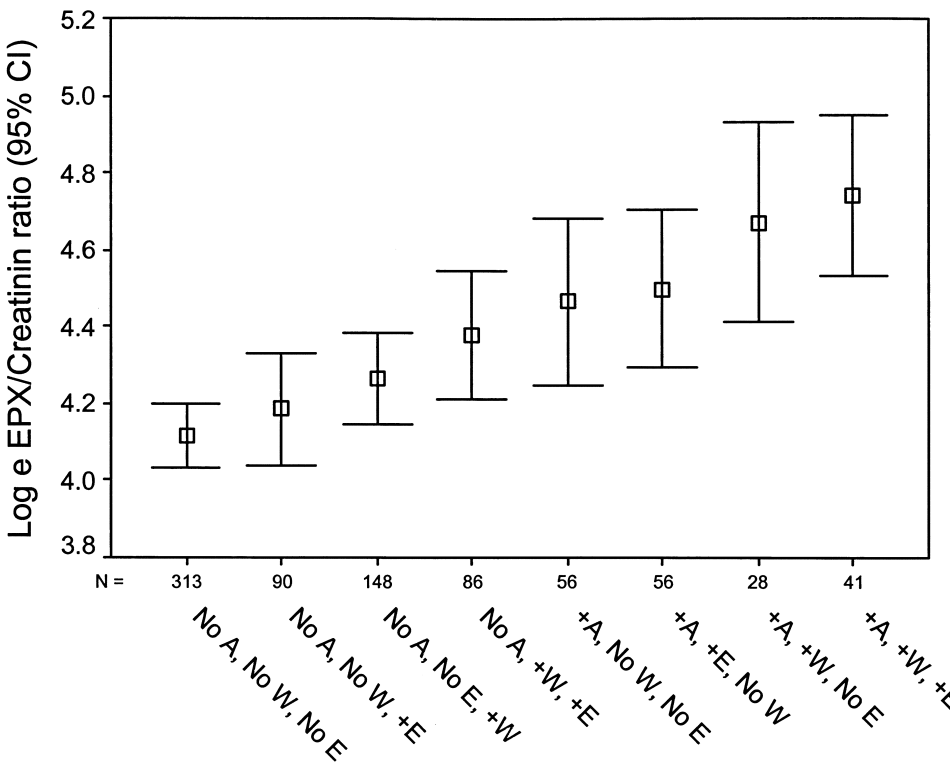
U-EPX values increased with increasing number of variables included (in keeping with Fig 2). When atopy, recent wheezing, cough (cold air), and eczema were included, the U-EPX values were affected as shown in Table IV.

Asthma, rhinitis, other
respiratory diseases



Cough and Recent Wheeze at Age 3 years

FIG 1. Relationship between U-EPX, cough, and wheezing.



Atopy (A), Wheeze (W) and Eczema (E) at age 3 years

FIG 2. Relationship between U-EPX, atopy, and symptoms suggestive of allergic diseases.

Asthma, rhinitis, other
respiratory diseases

TABLE II. Parentally reported symptoms and corresponding U-EPX levels

	Symptom-diagnosis	n	%		U-EPX/creatinine ratio (μg/mmol)		P value
					GM	95% CI	
Asthma, rhinitis, other respiratory diseases	Eczema at age 0-1 y	167	35.5	Yes	84.11	75.19-94.07	.008
		302		No	68.87	62.84-75.47	
	Eczema at age 1-3 y	302	33.4	Yes	79.49	73.03-86.54	.01
		601		No	69.19	65.06-73.58	
	Eczema still at age 3 y	222	24.5	Yes	82.94	75.33-91.32	.002
		681		No	69.36	65.46-73.51	
	Eczema at physical examination	137	15.2	Yes	89.04	78.61-100.86	.001
		766		No	69.86	66.18-73.75	
	Asthma at age 1-3 y	136	15.1	Yes	87.78	77.38-99.58	.001
		767		No	70.06	66.37-73.95	
	Asthma still at age 3 y	105	11.6	Yes	89.41	76.92-103.91	.003
		798		No	70.44	66.83-74.26	
	Asthma requiring medication	104	11.5	Yes	93.25	80.24-108.37	<.001
		799		No	70.08	66.49-73.87	
	Cough, more than others	187	20.7	Yes	88.75	80.04-98.41	<.001
		716		No	68.74	64.98-72.73	
	Cough, nighttime	347	38.4	Yes	77.58	71.58-84.08	.035
		556		No	69.47	65.19-74.02	
	Cough on exertion	144	16.0	Yes	84.36	74.93-94.98	.009
		759		No	70.42	66.67-74.39	
	Cough on excitement	87	9.6	Yes	84.45	72.88-100.18	.034
		816		No	71.22	67.58-75.06	
	Cough on exposure to cold air	93	10.3	Yes	96.45	82.37-112.93	<.001
		810		No	70.14	66.57-73.91	
	Wheezing ever at 3 y	333	36.8	Yes	80.22	74.08-87.09	.002
		571		No	68.78	64.11-72.72	
	Wheezing in last 6 mo	191	21.2	Yes	85.56	76.97-95.11	.001
		712		No	69.32	65.54-73.34	
	Wheezing requiring medication	247	27.2	Yes	80.33	73.11-88.24	.013
		656		No	69.75	65.76-73.96	
	Wheezing with cold air	40	4.4	Yes	98.36	75.32-128.44	.01
		863		No	71.46	67.93-75.17	
	Wheezing on exertion	64	7.1	Yes	90.94	74.79-110.56	.014
		839		No	71.24	67.66-75.00	
	<3 attacks of wheezing with SOB	135	15.0	Yes	85.14	74.98-99.67	.008
		768		No	70.46	66.75-74.37	
	Wheezing with colds	289	32.0	Yes	80.72	73.91-88.15	.004
		615		No	68.90	64.87-73.19	

SOB, Shortness of breath.

DISCUSSION

The precise role of U-EPX in the diagnosis and monitoring of allergic disease remains controversial.^{3-5,10-17} We have found a significant association of U-EPX with atopy and symptoms suggestive of allergic disease in 3-year-old children. Like others, we observed a difference in U-EPX levels between healthy boys and girls.¹² This finding remains unexplained but might warrant the setting of separate normal ranges for male and female patients.¹² U-EPX levels can be affected by circadian rhythm, concomitant respiratory infections, and ICSs.^{4,16-19} We cannot rule out the effect of circadian variation because some children did not provide a morning specimen. However, we would expect the observed associations to be even stronger if all specimens had been collected in the morning, when levels are highest.^{18,19} Concomitant mild upper respiratory tract infections did

occasionally occur, but the results were the same in the analysis including only those children who were well on the day. ICS use was not significantly associated with increased U-EPX levels, whereas sole use of a bronchodilator was associated. This is in keeping with previous reports that ICS use decreases U-EPX levels.^{4,17} Only 39 of 903 children received ICSs, and results did not change when they were excluded from analysis.

We have observed a very strong association between atopy and increased U-EPX levels. This is in agreement with the results of most previous studies,^{12,15,16} although some investigators did not see any effect of atopy.^{14,17} However, the latter studied comparatively small selected groups or symptomatic individuals.^{4,11,13} An important question is the relative contribution of atopy and symptoms to U-EPX levels.^{12,16} Oymar et al¹⁵ and Oymar and Bjerknes²⁰ reported that the effect of atopy was stronger than that of atopic dermatitis and postulated that a “non-

TABLE III. Main factors in multivariate analysis associated significantly with increased U-EPX levels

Variables included in ANOVA model	P value	F value	Significant interactions	P value	F value
Atopy	<.001	27.949	—		
Cough more than others	.006	7.544	—		
Wheezing ever	.045	4.037	—		
Eczema in clinic	NS (.066)	3.395	—		
Atopy	<.001	27.095	Atopy and eczema	.04	4.242
Cough in cold air	.002	9.464	Atopy, cough, and eczema	.042	2.753
Wheezing ever	.015	5.952	—		
Eczema in clinic	.043	4.117	—		
Atopy	<.001	27.780	Atopy, cough, and older sibling	.013	3.181
Cough more than others	.006	7.498	—		
Older siblings present	.006	7.710	—		
Sex	.019	5.530	—		
Wheezing ever	NS (.099)	2.734	—		
Eczema in clinic	NS (.09)	2.879	—		

All factors that were significant in *t* tests were entered in the model, but only the strongest factors are presented here. Very similar results were seen with the variable “recent wheezing.”
NS, Not significant.

dermal” focus of eosinophilic inflammation might be a contributing factor. This nondermal focus could be the gut mucosa (especially in infancy, when sensitization to food allergens prevails)²¹ or, alternatively, the airways.

If asymptomatic but sensitized children have increased eosinophilic inflammation, as suggested by raised markers, this could mean our tools are not sensitive enough to pick up the focus. We have previously reported that at age 3 years, atopic asymptomatic children had poorer lung function compared with that of nonatopic asymptomatic children, suggesting an underlying but still asymptomatic inflammatory process.⁶ However, in the current study *sR_{aw}* did not correlate with U-EPX levels. Other studies (using different lung function measures) have seen associations with U-EPX and lung function but usually with acute disease or when measured as a change from baseline after bronchodilator therapy.^{4,12,16,22}

The theory that subclinical airway inflammation might contribute to increased U-EPX levels in asymptomatic atopy is supported by our findings that sensitization to inhalant allergens is strongly associated with higher U-EPX levels. A possible pro-inflammatory contribution of inhalant allergens would be in keeping with the previous observation that inhalant (perennial > seasonal) sensitization was significantly associated with increased U-EPX levels.¹² Some authors found that eosinophilic cationic protein and EPX levels in nasal lavage fluid collected in the neonatal period from high-risk infants predicted a physician-diagnosed “wheezy bronchitis” during the first 6 months of life.^{23,24}

In our study a history of respiratory symptoms and physician-diagnosed asthma were significantly associated with increased U-EPX levels, especially when suggestive of airway hyperresponsiveness. Although wheezing and asthma are known to be associated with increased EPX,^{4,12,17,25} only 2 studies have reported increased U-EPX levels with symptoms of chronic cough.^{11,12,16,17} Labbe et al¹⁷ found that children with chronic cough (>3 months’ duration) had significantly

TABLE IV. Example of increasing U-EPX levels* with increasing symptoms in an ANOVA model

Variable	U-EPX/creatinine, GM (μg/mmol)
Negative to all	61.58
Recent wheezing only	72.19
Eczema only	72.59
Cough only	83.17
Atopy only	86.44
Atopy, recent wheezing, eczema, and cough	169.73

*Derived from estimated marginal means in ANOVA.

increased U-EPX levels compared with those of healthy control subjects, but the levels were not as high as those seen in children with symptomatic steroid-naïve asthma. They saw a trend of decreasing U-EPX levels when children with chronic cough were treated with ICSs or ketotifen, whereas in asthmatic children U-EPX levels decreased significantly after ICSs were commenced.

Is it possible that many children with chronic cough have airway hyperreactivity and possibly early cough-variant asthma? This theory would be supported by evidence of increased eosinophilic inflammation (greater U-EPX levels) and our finding of a significant association of cough and increased *sR_{aw}* (unpublished data). Our observation that parentally reported cough symptoms are associated with increased U-EPX levels more strongly than reported wheezing might be due to the difficulty parents can have with identifying wheezing correctly,^{6,26,27} whereas cough is easier to identify, especially in very young children. U-EPX measurement could be useful in the diagnosis of allergic airway disease in this very young age group, in which reliable symptom reporting is not always possible and acceptance of invasive tests is poor. However, sensitivity and specificity of U-EPX measurement are insufficient for use as a sole diagnostic tool because of a considerable overlap between symptomatic and asymptomatic children, as well as atopic and nonatopic children.

Asthma, rhinitis, other
respiratory diseases

In conclusion, in early childhood U-EPX levels reflect atopy and symptoms of atopic disease. Its role as an adjunct in the diagnosis and management of allergic airway disease, in particular cough-variant asthma in early childhood, might be important and requires further investigation.

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