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Predictors of exhaled nitric oxide (FeNO) in a large population-based sample of schoolchildren

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Introduction: Exhaled fractional nitric oxide (FeNO) is increasingly used in clinical settings as a non-invasive marker of airway inflammation. It is associated with asthma severity and asthma control, and is sensitive to corticosteroid treatment and to preventive measures.
Little is known, however, on determinants of FeNO in unselected children from the community. Some authors suggested that FeNO could not be used to assess asthma severity in the community, because it is strongly influenced by other atopic conditions[1]. Published studies have often not disentangled the associations between FeNO and ethnicity, atopy, asthma, lung function and anthropometric data.

Aims: To describe determinants of FeNO in a population-based sample of school children.

Methods

Population
A cohort of 3300 children (1950 whites and 1350 south Asians) aged 2 to 4 years in 1998 was randomly sampled from the population of Leicestershire, UK.[2,3] Parents completed postal questionnaires in 1998, 2001, and 2003.
In 2005, at age 9-12 years, all children whose parents had replied to the first survey and at to least 1 follow-up survey (N=2021) were invited to the laboratory. By September 2006, 509 children had performed FeNO measurements, skin prick tests (cat, dog, mixed grass and house dust mite), pre- and postbronchodilator spirometry and methacholine bronchial challenge.

Questionnaire
Data on symptoms and diseases during the past 12 months, and on environmental exposures were collected via a standardised parent-completed questionnaire.

Measurements
- FeNO, using the online single breath technique, measured according to ERS and ATS guidelines (Aerocrine Niox Mino)
- Pre- and postbronchodilator spirometry (Spirometer, Vitalograph Pneumotrac)
- Bronchial responsiveness using standard methacholine challenge by the Cockcroft protocol
- Skin-prick tests (house dust mite, animal dander, moulds, pollens). A child was defined as atopic if there was a wheal of >3 mm for at least one allergen.

Analysis
We analysed the association between FeNO and potential determinants using multiple linear regression. Likelihood ratio tests were used to test differences between groups and interaction terms were included to test for effect modifications.

Results

1) In univariate analysis, FeNO was strongly associated with south Asian ethnicity, atopy (skin prick test positivity), current eczema, current hayfever, severity of asthma (measured as numbers of attacks), BHR and forced vital capacity (**Table 1**). No association with age and weight were found.
2) Adjusting for other covariates in the multiple linear regression (**Table 2**), only atopy, asthma severity, and height remained strong predictors of FeNO, while there was a borderline association with eczema and forced vital capacity.
3) FeNO was strongly **associated with frequency of asthma attacks in atopic, but not in non-atopic children** (**Table 3**, p interaction <0.01).

Conclusion

- A strong association between FeNO and south Asian ethnicity in the unadjusted analysis was explained by the higher prevalence of of atopy in south Asian children and disappeard after adjustments.
- Similarly, a strong association between FeNO and hayfever and eczema disappeared after adjustment for atopy (skin prick tests). Hayfever and Eczema per se do not appear to increase FeNO in atopic children.
- In contrast, number of asthma attacks remained independent determinants of FeNO even after adjustment for atopy.
- In stratified analysis, frequency of asthma attacks were associated with FeNO only in atopic but not in nonatopic children. This suggests that FeNO might be a useful marker of asthma severity only in children with atopic asthma, and not in non-atopic asthma phenotypes (such as viral wheeze).

References

1. Welsh L, Lercher P, Horak E. Exhaled nitric oxide: interactions between asthma, hayfever, and atopic dermatitis in school children. *Pediatr Pulmonol* 2007:42(8):693-8
2. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (pre-school) children increasing in prevalence? *Lancet 2001;357: 1821-5.*
3. Kuehni CE, Brooke AM, Strippoli MPF, Spycher BD, Davis, A, Silverman M. Cohort Profile: The Leicester Respiratory Cohorts. *Int J Epidemiol, in press.*

Table 1: FeNO (ppb) in the study population by selected characteristics (unadjusted analysis, n=491)
The first line can be read as follows: the mean FeNO is 17.4 in white children and 25.7 (17.4 + 8.3) in south Asian children

	Geometric mean (baseline)*	Change F_{ENO}	p
South Asian vs. Whites	17.4	8.3	<0.01
Male gender vs. female	18.7	1.4	0.31
Height (cm) †	19.4	0.1	0.36
Any positive SPT vs. none	13.8	16.2	<0.01
Eczema vs. no Eczema	17.0	7.0	<0.01
Hayfever vs. no Hayfever	16.3	11.1	<0.01
Mild/severe BHR vs. borderline/normal‡	17.9	6.5	<0.01
Forced Expiratory Vital Capacity (l) ††	19.3	-3.0	0.03
Frequency of attacks of wheeze			<0.01
1-3 attacks vs. none	16.7	9.9	
>3 attacks vs. none	16.7	17.7	

* FeNO for reference category
† average height =145 cm; FeNO change per additional cm
††average FVC = 2l; FeNO change per additional liter
‡ BHR assessed by PC_{20}: mild/severe BHR = PC_{20} concentration methacholine 1 to 4 mg/ml ; normal/borderline BHR = PC_{20} concentration methacholine 4 to 32 mg/ml.

Table 2: Association between F_{ENO} (ppb) and selected characteristics (adjusted analysis, n=491)

	Change F_{ENO}	p
	baseline 11.7†	
South Asian vs. Whites	1.6	0.26
Male gender vs. female	0.4	0.59
Height (per cm) ‡	0.3	<0.01
Any positive SPT vs. none	8.9	<0.01
Eczema vs. no	1.9	0.03
Hayfever vs. no	0.5	0.63
Mild/severe BHR vs. borderline/normal§	1.8	0.09
Forced Expiratory Vital Capacity (per l) ‡	-2.3	0.09
Frequency of attacks of wheeze		<0.01
1-3 attacks vs. none	3.5	
>3 attacks vs. none	8.6	

* adjusted for variables listed in table and age, weight, inhaled corticosteroids, mother smoking and type of diet.
† According to the model, children with **baseline characteristics** (white, female, average age, average height, average weight, non atopic, no eczema, no hayfever, borderline/normal BRH, average FVC, no current wheeze, no inhaled corticosteroids, no mother smoking, English diet) have a mean F_{ENO} of **11.7 ppb**.
‡ average height =145 cm; average FVC = 2l
§ BHR assessed by PC_{20}: mild/severe BHR = PC_{20} concentration methacholine 1 to 4 mg/ml ; normal/borderline BHR = PC_{20} concentration methacholine 4 to 32 mg/ml.

Table 3: Association between FeNO (ppb) and severity of wheeze by atopic status (adjusted* analysis, n=491)
P for interaction test (atopy*frequency of attacks)=<0.01

		Non atopic (n=276)			Atopic (n=215)	
	n	Change F_{ENO}	p	n	Change F_{ENO}	p
		baseline 13.7†			**baseline 15.5†**	
Frequency of attacks of wheeze			0.77			<0.01
1-3 attacks vs. none	27	-0.7		58	8.7	
>3 attacks vs. none	14	1.4		34	18.3	

* adjusted for ethnicity, gender, age, height, weight, eczema, hayfever, BHR, FVC, inhaled corticosteroids, mother smoking and type of diet.
† According to the model, children with **baseline characteristics** (white, female, average age (11 yrs old), average height (145 cm), average weight (40 kg), average FVC (2 l), no current wheeze, no inhaled corticosteroids, no eczema, no hayfever, normal BHR, no mother smoking, English diet) have a of **13.7 ppb** and **15.5 ppb** in non atopic and atopic group respectively.