

FACTORS ASSOCIATED WITH SERIAL LONGITUDINAL CHANGES IN EXHALED NITRIC OXIDE (FeNO) – A REVIEW OF THE LITERATURE

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ABSTRACT

It has been well documented that the major hallmarks of asthma are the presence of airway inflammation, variable airway obstruction and airway hyperresponsiveness (AHR). Fractional exhaled nitric oxide (FeNO) is a well-known inflammatory marker which has a potential role in the diagnosis and surveillance of those at risk of developing asthma, although its utility in occupational contexts is less clear. This review focuses on identifying the factors associated with longitudinal changes in FeNO in general asthmatic and working populations. The review found that exposure to allergens (common aeroallergens and occupational allergens) or their avoidance, as well as asthma-education programmes (especially those focusing on adherence to inhaled corticosteroid usage) are associated with longitudinal changes in FeNO. Other host-associated factors such as baseline lung function (FEV₁), atopy status and smoking need further evaluation in order to assess their impact on serial longitudinal changes in FeNO.

INTRODUCTION

The presence of airway inflammation, variable airway obstruction and airway hyperresponsiveness (AHR) as major hallmarks of asthma has been well documented.¹ Among this triad, airway inflammation appears to be increasingly recognised as a major component in the initiation and long-term progression of the disease. Airway inflammation in asthma is measured using several methods, one being the measurement of fractional exhaled nitric oxide (FeNO) as a marker for asthma in symptomatic individuals.² FeNO is a non-invasive marker that has been extensively investigated in several contexts such as diagnosis, initiating treatment, tailoring medication, achieving asthma control and predicting future relapses of asthma. Various studies have demonstrated that FeNO is affected by individual host attributes and environmental factors. FeNO levels at baseline are reported to be higher in men than in women and levels increase with height, atopy, dietary intake of food rich in nitrates, allergen exposures causing sensitisation, and viral airway infections.³⁻⁶ FeNO levels can be decreased with bronchoconstriction and inhaled corticosteroid therapy, and among both active and passive smokers.³⁻⁶ Most of the studies on the determinants of baseline FeNO have focused on the asthmatic population; fewer studies have evaluated serial changes in FeNO in the general population or in occupational contexts over longer periods of time.

The aim of this review is to identify the determinants of serial longitudinal changes in FeNO and to determine its usefulness in predicting increased asthma risk. Furthermore, this review could also contribute towards developing greater insights into studies of the applicability of FeNO in predicting long-term asthma outcomes and lung function deficits in those with persistent exposures to respiratory sensitisers. It could also contribute developing greater understanding of the clinical improvements in individuals subjected to treatment or exposure interventions. The review includes all the relevant epidemiological or experimental studies on asthmatic children or adults having a direct or indirect allergen exposure modulation component that were published in English between January 1999 and April 2017. Articles were retrieved from PubMed/Medline and Google Scholar. The key search terms that were used in this review were 'asthma', 'FeNO' or 'exhaled nitric oxide' plus either 'serial' or 'longitudinal'. Furthermore, some articles were retrieved using the functions 'similar articles search' in PubMed and 'related articles' in Google Scholar as well relevant articles that were cited in the references of these articles. Clinical studies that focused on the effect of medication or an inhalation challenge test on FeNO in patients were excluded from this review.

The review identifies various factors associated with

longitudinal changes in FeNO in 20 studies as outlined in Tables I–III. The articles were summarised according to the population of interest. Eight of the studies were experimental in design, with six being quasi-experimental studies and two being non-randomised controlled trials. Furthermore, there were ten epidemiological studies (five longitudinal, four case-control and one cross-sectional) and two clinical case reports. Most of the studies focused on asthmatic populations but two studies also evaluated FeNO in working populations with exposure to respiratory sensitisers (Figures 1a–c).

ENVIRONMENTAL FACTORS

ALLERGEN EXPOSURES

Various studies using specific inhalation challenges (SIC) of suspected allergens in general asthmatic patients have shown that it takes up to eight hours before FeNO starts to increase and that it continues to remain elevated for up to 48 hours^{27,28} – in some studies up to 72 hours.^{29,30} In patients suspected of having occupational asthma, most studies have reported changing FeNO levels 20–24 hours post-SIC^{25,30–36} and showed a significant increase in FeNO.²

Exposure to the relevant allergen in asthmatic populations has demonstrated positive associations with longitudinal changes in FeNO. Baraldi et al,¹⁶ in their case-control

study investigating the association between serial FeNO and exposure to grass pollens in atopic asthmatic children sensitised to grass pollen, found that exposure in the pollen season led to a two-fold increase in the overall mean FeNO levels. These levels returned to baseline after the season. This association between exposure to in-season pollen and to other allergens was also reported by Roberts et al,¹⁹ Spanier et al²⁰ and Cutts et al.²¹ However, Fowler et al²⁶ found a negative association between allergen exposure and FeNO (1.5-fold mean decrease, 95% CI 1.2–1.7 fold, $p < 0.001$). Since exposure was not monitored during the long study period, changes in the exposure level over this period may have occurred that may have introduced bias in the study.

Ongoing exposure to an occupational allergen appears to be one of the determinants of longitudinal change in FeNO. Van der Walt et al evaluated serial FeNO associated with occupational exposure to spices in 150 mill workers after a two-day exposure-free period during time off work.²⁵ No significant difference in the overall mean FeNO between baseline, after the shift and 24 hours after the baseline pre-shift level was recorded. However, there was a >12% increase in FeNO across the 24-hour period in 23% of the workers. The authors concluded that exposure to the spice allergens in this occupational setting was associated with a delayed increase in FeNO from the baseline. Hewitt et al also evaluated serial FeNO among workers exposed to laboratory animal allergens (LAA).²⁴ The investigators studied 50 workers in an animal laboratory for five working days after being off work for two days. There was a progressive increase in FeNO over the working week in one subject who was seropositive to one or more of the LAA. In addition, three subjects experienced >25 ppb fluctuation in FeNO during the working day in the period of observation. Both of these studies were conducted in worker populations comprising both asymptomatic and symptomatic individuals.

ALLERGEN EXPOSURE AVOIDANCE

Avoidance of exposure to the suspected common



Figure 1a-b: Measurement of exhaled nitric oxide (FeNO) in a study of spice mill and bakery workers in Cape Town



Figure 1b



Figure 1c: Measurement of exhaled nitric oxide (FeNO) in a study of asthma among school children in Cape Town

TABLE I: EXPERIMENTAL STUDIES OF SERIAL LONGITUDINAL FeNO MEASUREMENT AMONG ASTHMATICS IN THE GENERAL POPULATION (CHILDREN AND ADULTS)

TABLE IA: STUDIES AMONG CHILDREN			
AUTHORS	PIACENTINI ET AL, 1999 ⁷	PIACENTINI ET AL, 2001 ⁸	PERONI ET AL, 2002 ⁹
AIM OF STUDY	To evaluate the effect of house-dust mite (HDM) avoidance in allergic asthmatic patients on FeNO.	To determine the relationship between exposure level to house-dust mite (HDM) allergen and the magnitude of exhaled FeNO after allergen avoidance in a group of allergic asthmatic children.	To study the change in lung volumes and airway inflammatory markers in house-dust mite (HDM) sensitised asthmatic children resident in an allergen free environment.
STUDY DESIGN	Quasi-experimental	Quasi-experimental	Quasi-experimental
STUDY POPULATION	20 Italian asthmatic children (6–15 years) sensitised to HDM. Thirteen received regular courses of inhaled corticosteroids (ICS).	14 Italian asthmatic children (6–15 years) sensitised to HDM.	18 asthmatic children who have moderate to severe asthma and sensitised to HDM.
INTERVENTION	Avoidance of HDM by staying at 1 756 m above sea level in the Italian Alps for three months.	Avoidance of HDM by staying at 1 756 m above sea level in the Italian Alps for three months.	Avoidance of HDM by staying at 1 756 m above sea level in the Italian Alps for nine months between September and June.
OUTCOME MEASURES	Change in FeNO level.	- The level of HDM group I allergen at home. - Change in FeNO.	FeNO, lung function.
MEASUREMENTS	- FeNO was measured daily, always at the same hour starting at the parents' house (T0), for two weeks after moving to the residential home until day 15 (T1), after three months at the residential campus (T2), and, in 10 of the 20 patients, two weeks after return to their parents at sea level (T3). - FEV₁ is measured at T0, T1, T2, and T3. - Serum eosinophil cationic protein (ECP) was measured at T0, T2, and T3.	- Children received a regular course of ICS for at least three months at the beginning of the study. The ICS course was gradually withdrawn in all the subjects. By T1, none of the children received any ICS for one month at least. - FeNO was measured at the parent's home (T0) and after three months at the residential campus (T1).	- Measurements taken (i) within three days of admission, (ii) after 3 months of stay, (iii) within two days before leaving the residential home for the Christmas holiday, (iv) on return to the residential home after 15 days at home and (v) at the end of the camp after nine months of staying at residential home. - ICS were withdrawn after few weeks of admission, resumed during the Christmas holiday and withdrawn again during the rest of the study.
RESULTS	- FeNO decreased ($p = 0.014$ at T1) with a significant effect of the time in the first two weeks ($p = 0.026$). It didn't change in the period T1 to T2, and returned to T0 level at ($p = 0.004$, T2 vs T3). - FeNO did not change significantly from T1 to T2, despite the withdrawal of ICS. - FEV₁ improved gradually.	Strong correlation between the change in FeNO (T0–T1) and the levels of HDM antigens in the beds of the patients before T0; $r = 0.618$ ($p = 0.026$).	- FeNO decreased from (21.3 ± 3.9 ppb) in September to (11.9 ± 1.7 ppb) in December ($p = 0.03$). No significant change after the holiday in January (12.5 ± 2.6 ppb) nor at the end in June (13.2 ± 2.0 ppb). - The RV to TLC ratio decreased between September and December ($p = 0.003$), increased between December and January ($p = 0.002$) and decreased again between January and June ($p = 0.002$). - No significant correlation between FeNO and lung volumes.
LIMITATIONS	- Absence of a control group at sea level. - Small sample size. - Independent effect of high altitude on FeNO levels. - No mention of important confounders (passive smoking and diet).	- Absence of a control group at sea level. - Small sample size. - Independent effect of high altitude on FeNO levels. - No mention of important confounders (passive smoking and diet).	- Absence of a control group at sea level. - Small sample size. - Independent effect of high altitude on FeNO levels. - No mention of important confounders (passive smoking and diet).
CONCLUSION	FeNO levels decreased over time after the avoidance of the potential allergen in allergic asthmatic children.	FeNO reduction after the avoidance of the potential allergen correlated with the magnitude of the exposure of the allergen prior to avoidance.	Allergen avoidance at high altitudes led to a reduction in FeNO levels in asthmatic children sensitised to HDM.

TABLE IA: STUDIES AMONG CHILDREN (CONTINUED)

AUTHORS	HUSS-MARP ET AL, 2007 ¹⁰	KAMINSKY ET AL, 2008 ¹¹	SAITO ET AL, 2013 ¹²
AIM OF STUDY	To study effect of rehabilitation of asthmatic children at high altitudes and HDM avoidance on asthma control.	To study effect of attending an asthma summer camp on airway inflammation as measured by FeNO.	- To examine whether an asthma education program is associated with asthma control. - To compare absolute levels and changes of ACT score, FEV₁, and FeNO over a year after the intervention. - To evaluate FeNO as a marker of asthma control compared to other methods.
STUDY DESIGN	Quasi-experimental	Quasi-experimental	Quasi-experimental
STUDY POPULATION	311 asthmatic children with increased FeNO levels at admission (>17 ppb).	27 asthmatic children.	12 mild, 21 moderate, and 17 severe persistent asthmatic adult patients (n = 50) with poor adherence to medication.
INTERVENTION	Rehabilitation at 1 200 m above sea level in the Bavarian Alps.	Participation in a one-week camp during the summer of 2006 in the United States.	Asthma education programme providing information about asthma pathogenesis, diagnosis, severity, medications (including side-effects), differences between reliever and controller agents, importance of asthma treatment, inhaler-device instructions, exacerbation management, peak expiratory flow (PEF) monitoring, and a self-management plan.
OUTCOME MEASURES	Change in FeNO level.	FeNO, lung function and ACQ score.	Change of ACT score, FeNO and spirometry levels over time.
MEASUREMENTS	- Subjects were grouped according to asthma severity based on the clinical features before therapy from grade I (mild intermittent) to three levels of persistent asthma (grades II–IV: mild, moderate, and severe, respectively; grade I: n = 67; grade II: n = 135; grade III: n = 104; grade IV: n = 5). - FeNO measurement was performed on the day of admission and at discharge (4–6 weeks).	- FeNO, FEV₁, and ACQ score were measured at the beginning and end of the week. ACQ score was also obtained at one month and six months after the camp. - The children participated in daily educational activities about asthma.	- Subjects were reviewed four times: at entry and at intervals of three, six and 12 months. - Treatment was not changed in the first three months to study the effect of the educational programme on asthma control. Thereafter, the treatment could be changed according to the GINA guidelines. - During the follow-up period, subjects were divided into two groups: - Stable group: treatment had not changed or was decreased over the study period. - Unstable group: increase in ICS dose or other anti-asthmatic drugs added during the study period.
RESULTS	47.2% reduction in the mean FeNO of all 311 children after rehabilitation, with 38.5 ± 22.8 ppb at admission compared to 20.1 ± 13.2 ppb at discharge ($p < 0.001$). - FeNO reduction was significant in all subgroups and most marked in children with mild asthma. - FeNO reduction in asthmatics with isolated HDM sensitisation was no different to the reduction in other children sensitised to other allergens.	- FeNO dropped significantly by 45% ($p < 0.001$), but the changes in lung function and ACQ was not statistically significant. - Among the 21 children prescribed with ICS, 18 had decreased FeNO and three had increased FeNO. - Among the four children not prescribed any ICS, three had decreased FeNO, and one had an increase in FeNO.	- Decrease in FeNO and increase in ACT scores in the stable asthma group (n = 42) compared with the unstable asthma group (n = 8); ($p < 0.001$) and remained consistent in the stable group over the course of 12 months. - Significant correlations between change in FeNO, ACT score and FEV₁ in all four visits.
LIMITATIONS	- Absence of a control group at sea level. - HDM concentrations in the rehabilitation centre not reported. - Independent effect of high altitude on FeNO levels. - No mention of important confounders (passive smoking and diet).	- Small sample size. - First-day measurements were conducted in the afternoon and the final-day measurements in the morning.	- Selection bias. - Hawthorne effect.
CONCLUSION	FeNO decreased significantly after 4–6 weeks rehabilitation at high altitude, which could be explained by allergen avoidance, absence of air pollution and improved compliance to medication.	FeNO levels declined after attendance of a one-week asthma summer camp, despite no changes in lung function or asthma control, which could be explained by allergen avoidance, absence of exposure to tobacco smoke, and avoidance of psychosocial stressors.	- FeNO levels declined after an asthma education program and remained significant over a year. - Change in FeNO levels correlated significantly with change in ACT score and change in FEV₁ levels.

TABLE IB: STUDIES AMONG ADULT WORKING POPULATION

AUTHORS	DRESSEL ET AL, 2007 ¹³	DRESSEL ET AL, 2009 ¹⁴
AIM OF STUDY	To assess whether FeNO is useful in detecting a reduction in airway inflammation within a few weeks of an educational intervention in farmers with occupational asthma.	To determine whether long-term changes in FeNO could be detectable a year after an intervention.
STUDY DESIGN	Non-randomised controlled trial	Non-randomised controlled trial
STUDY POPULATION	Cases: 81 animal farmers with occupational asthma sensitised to cow dander and storage mites who participated in a one-day educational program. Controls: 24 animal farmers with occupational asthma not subjected to an intervention.	- Cases: animal farmers with occupational asthma (n = 43) who participated in a one-day educational program. - Control: animal farmers with occupational asthma (n = 15) not subjected to an intervention.
INTERVENTION	A one-day educational programme provided general information about the pathogenesis of asthma and allergies, environmental influences, treatment, major occupational allergens causing asthma, particularly cow dander and mites, and prevention methods in the workplace.	A one-day educational programme provided general information about the pathogenesis of asthma and allergies, environmental influences, treatment, major occupational allergens causing asthma, particularly cow dander and mites, and prevention methods in the workplace.
OUTCOME MEASURES	FeNO, lung function and a questionnaire.	FeNO, lung function and a questionnaire.
MEASUREMENTS	Baseline FeNO measurement and repeated 4–6 weeks after the intervention.	Baseline FeNO measurement and repeated one year after the intervention.
RESULTS	- There was a decline in the proportion of subjects reporting at least one current respiratory symptom at work (p = 0.012) in the intervention group. - The geometric mean FeNO decreased from 28.2 to 25.7 ppb (p = 0.042). - Subjects with a baseline FeNO of >35 ppb (n = 32), FeNO decreased from 59.7 to 49.2 ppb (p = 0.003). - There was no significant change in the pulmonary function test after the intervention.	- Geometric mean $\pm$ SEM of FeNO decreased from (31.5$\pm$1.1) to (25$\pm$1.1) ppb in the intervention group (p = 0.001), while it showed a slight but statistically insignificant increase in the control group (p = 0.258) - FEV₁ and FEV₁/FVC did not significantly change over time in either group.
LIMITATIONS	- Selection bias. - No mention of important confounders (atopy and diet).	- Selection bias. - No mention of important confounders (atopy and diet).
CONCLUSION	FeNO showed a significant short-term reduction after an educational intervention in animal farmers with workplace-related allergic asthma, which was accompanied by decrease of frequency of symptoms.	FeNO showed a significant long-term reduction after an educational intervention in animal farmers with workplace-related allergic asthma, which may be explained by a reduction in allergen exposure.

TABLE II: EPIDEMIOLOGICAL STUDIES OF SERIAL LONGITUDINAL FeNO MEASUREMENT AMONG ASTHMATIC CHILDREN

AUTHORS	BARRETO ET AL, 2008 ¹⁵	BARALDY ET AL, 1999 ¹⁶
AIM OF STUDY	To assess variations and reproducibility of FeNO in subjects maintained under similar environmental conditions.	To evaluate the relationship between natural allergen exposure to grass pollen and the changes in FeNO in atopic asthmatic children during and out of the grass pollen season.
STUDY DESIGN	Case-control	Case-control
STUDY POPULATION	29 children (12 healthy subjects and 17 asthmatics with good control). - Asthmatics divided into two groups; corticosteroids-naïve (n = 9) and corticosteroids-treated (n = 8). - All asthmatics were atopic.	21 grass pollen sensitised children (age 6–16 years) with a seasonal allergic asthma. 21 non-atopic healthy children age and sex matched with the asthmatics.
INTERVENTION/ EXPOSURE	One-week stay in a countryside sanatorium situated in a wooded area near the Tatra mountains at an altitude of 970 m.	Followed up and monitored before (March), during (May), and after (November) the pollen season.
OUTCOME MEASURES	FeNO, lung function.	FeNO, lung function.
MEASUREMENTS	- On arrival, all subjects underwent a clinical examination and a history recorded of symptoms and therapy. Spirometry and FeNO measurements done on all subjects twice a day for the first two days and again at 8:00 am on day seven. - All participants avoided food intake and physical exercise for at least two hours before testing. - Participants excluded from the study if unsatisfactory lung function maneuvers or respiratory symptoms developed during the weekly follow-up.	- All patients underwent physical examination, spirometry and measurement of FeNO on three occasions: before (March), during (May) and after the grass pollen season (November). On each occasion, measurements were performed in the afternoon. - The atmospheric pollen counts were conducted throughout the year using a volumetric spore trap and daily mean concentration recorded and expressed as pollen grains per m³ of air per 24 hrs.

AUTHORS	BARRETO ET AL, 2008 ¹⁵	BARALDY ET AL, 1999 ¹⁶
RESULTS	- At baseline, the worst lung function observed among corticosteroid-treated asthmatics and the highest FeNO values recorded in corticosteroid-naïve asthmatics. - The differences in FeNO at baseline between asthmatics versus healthy participants was significant only among corticosteroid-naïve patients. - Differences in lung function between the groups remained unchanged at each session. - FeNO levels among corticosteroid-naïve as well as treated asthmatics decreased over time and became statistically non-significant (vs healthy subjects) at the last session (day 7). - No intra-group differences were found between nocturnal and diurnal FeNO in all the groups.	- ICS therapy was not altered through the pollen season for all subjects. - The mean value of FeNO before the grass pollen season (March) was (12.7 ± 5.1 ppb) and was significantly higher ($p < 0.001$) when compared to healthy subjects (7.8 ± 2.7 ppb). - In the pollen season (May) there was a significant ($p < 0.001$) two-fold increase in FeNO (21.4 ± 7.6 ppb) with respect to pre-season baseline values. - After the season (November), FeNO returned to pre-seasonal values (12.8 ± 5.8 ppb). - Non-relationship was found between the changes in FeNO and changes in symptom scores. - No significant changes in lung-function parameters during and after the pollen season.
LIMITATIONS	- Small sample size. - High altitude and climate may affect the results. - No mention of important confounders (passive smoking and diet). - There was no intra-group analysis to study the significance of the mean difference between day 1 and day 7.	- Small sample size. - No FeNO measurements taken for the control group during and after the pollen season. - No mention of important confounders (passive smoking and diet).
CONCLUSION	FeNO decreased a week after allergen avoidance at high altitude.	Natural allergen exposure during the grass season resulted in an increase in FeNO in asthmatic children which then returned to the level of the pre-seasonal range after the season passed.

TABLE II: EPIDEMIOLOGICAL STUDIES OF SERIAL LONGITUDINAL FeNO MEASUREMENT AMONG ASTHMATIC CHILDREN (CONTINUED)

AUTHORS	ADAR ET AL, 2015 ¹⁷	HOLGUIN ET AL, 2015 ¹⁸
AIM OF STUDY	To assess variability in FeNO in children in relation to exposures to diesel pollution from school buses.	To assess effects of traffic emissions on FeNO in children with and without asthma.
STUDY DESIGN	Case-control.	Case-control.
STUDY POPULATION	275 children riding on diesel school buses, with a mean age of 9.5 years. 148 were asthmatics, and 127 were healthy subjects.	200 children (age 6–12 years), 50% had physician-diagnosed asthma, and 50% were healthy subjects.
INTERVENTION/ EXPOSURE	Children riding on school buses were monitored before, during and after the adoption of clean-fuel technology, such as diesel oxidation catalysts (DOCs), closed crankcase ventilation systems (CCVs), ultralow-sulfur diesel (ULSD), and biodiesel.	Children were monitored over a four-month period to determine the effects of road and traffic densities, carbon and particulate matter on FeNO levels.
OUTCOME MEASURES	FeNO, lung function, air pollution levels on school buses.	FeNO, traffic-related air pollution levels, traffic densities.
MEASUREMENTS	- Children were assessed an average of six times over four years. - Lung function and FeNO were measured during monthly data collection sessions at the schools. - Fine and ultra-fine particles (UFP) were measured inside 188 buses during 597 commutes.	- Children were assessed with spirometry, FeNO, and skin-allergy testing bi-weekly over four months. - Daily respiratory health questionnaires were completed by parents. - Road-density (amount of road length in kilometres in each buffer) and traffic density (vehicle-km/h) within buffer areas around study schools and subject homes were measured. - Air pollution was measured at the schools as follows: 48-hour average of less than $2.5 \mu\text{m}$ (PM_{2.5}) particulate matter and elemental carbon measurements. - Weekly NO₂ measurements.
RESULTS	- Higher FeNO levels were observed among children with asthma, compared to healthy children. - Buses with ULSD were associated with reduction in UFP (−47%; 95% CI, −58 to −34%). - Buses with ULSD were associated with 16% lower FeNO, particularly in asthmatics.	- Higher road density was associated with increased FeNO and reduced FEV₁ in asthmatics. - No association was observed between fine particulate matter (PM_{2.5}) or elemental carbon and FeNO.
LIMITATIONS	- Potential for important confounding by time (some technologies used only later in the study). - No mention of important confounders (atopy and diet).	- Differences in measurement frequencies of PM_{2.5} and NO₂ could have affected results. 48-hour PM_{2.5} measurements may not precisely capture daily pollution fluctuations.
CONCLUSION	Adoption of cleaner school bus diesel-emission technologies reduced childrens' exposure to fine and ultra-fine particles, which was associated with a decrease in FeNO levels, particularly in asthmatics.	Increased traffic exposure leads to increased FeNO, particularly in asthmatics.

TABLE II: EPIDEMIOLOGICAL STUDIES OF SERIAL LONGITUDINAL FeNO MEASUREMENT AMONG ASTHMATIC CHILDREN (CONTINUED)

AUTHORS	ROBERTS ET AL, 2004 ¹⁹	SPANIER ET AL, 2004 ²⁰	CUTTS ET AL, 2013 ¹²
AIM OF STUDY	To evaluate effect of pollen on FeNO in children with seasonal asthma.	To evaluate seasonal and environmental effects on FeNO in tobacco-exposed children with asthma.	To evaluate variability in FeNO over a ten-month period in children with and without asthma.
STUDY DESIGN	Longitudinal study.	Longitudinal study.	Longitudinal study.
STUDY POPULATION	44 children (age 6–16 years) with seasonal allergic asthma.	225 children (age 6–12 years) with physician-diagnosed asthma.	• 178 primary school children, with a mean age of 9.6 years (SD = 1.3 years). • 47 were asthmatics, and 131 were healthy subjects.
INTERVENTION/EXPOSURE	Exposure to pollen during the pollen season.	Evaluated at baseline, six and 12 months and assessed for environmental exposures.	Monitored over a ten-month period and assessed for environmental exposures.
OUTCOME MEASURES	FeNO, lung function, daily asthma symptoms.	FeNO, settled dust allergens (SDA), indoor airborne particles (IAP), allergen sensitisation, tobacco smoke exposure.	FeNO, lung function, daily asthma symptoms questionnaire.
MEASUREMENTS	• Evaluated before the pollen season; then at regular four-weekly intervals throughout one pollen season. • All patients underwent physical examination, spirometry and measurement of FeNO. • Atmospheric pollen counts were taken throughout the pollen season with a seven-day volumetric spore trap.	• FeNO measured. • Dust mite, dog, cat and cockroach allergens measured with monoclonal ELISA. • Indoor particulate matter measured. • ImmunoCap for allergen sensitisation. • Tobacco smoke exposure measured with using a survey, biomarkers (hair and serum cotinine) and a nicotine dosimeter.	FeNO measured at two-month intervals, on between four and six different occasions (851 measurements) as follows: • 86 children measured on six occasions; • 51 children measured on four occasions. • 21 children measured on four occasions.
RESULTS	• There was a significant increase in median FeNO during the pollen season (9.2 ppb) compared to before the pollen season (6.2 ppb) ($p = 0.002$). • There was a significant relationship between standardised FeNO and pollen counts on the day of measurement ($p < 0.01$). • No significant changes were seen in lung-function parameters before or during the pollen season.	• Significant associations were seen between longitudinal change in FeNO and baseline FeNO. • Lowest and highest FeNO levels were seen in winter and autumn (fall), respectively ($p = 0.002$). • Being atopic lead to increased FeNO levels. • Cat and dust mite allergen levels significantly increased FeNO. • Airborne nicotine significantly decreased FeNO. • FeNO was not associated with passive smoking exposure when measured by biomarkers and reported smoking by parents.	• Significant associations were seen between initial FeNO concentrations and future values. • FeNO increased during the pollen session (increase in log transformed FeNO 1.34 [95% CI 1.05–1.70]) and elevated also in those with mould at home during September–October.
LIMITATIONS	• Small sample size. • Absence of a control group of children without seasonal asthma. • No mention of important confounders (daily activities, and diet).	• Absence of a control group of children not exposed to tobacco smoke. • Settled dust allergens were only measured at baseline.	• Uneven numbers of measurements taken on different sample groups. • No mention of important confounders (daily activities and diet).
CONCLUSION	Natural allergen exposure during the pollen season increased FeNO in asthmatic children.	Environmental triggers, airborne nicotine, and baseline allergen sensitisation affected FeNO levels.	Both baseline FeNO values and intervals between FeNO measurements were related to individual FeNO values, irrespective of asthma status.

TABLE III: EPIDEMIOLOGICAL STUDIES AND CASE REPORTS OF SERIAL LONGITUDINAL FeNO MEASUREMENT IN ADULTS

TABLE IIIA: EPIDEMIOLOGICAL STUDIES AMONG ADULTS AND WORKING POPULATIONS

AUTHORS	HEWITT ET AL, 2008 ²⁴	VAN DER WALT ET AL, 2016 ²⁵	FOWLER ET AL, 2009 ²⁶
AIM OF STUDY	To assess whether serial FeNO measurements may detect exposure-related inflammation in laboratory animal workers.	To evaluate association between FeNO and occupational exposures to spices.	To assess whether exposure to common domestic allergens affects long-term FeNO measurements in adult asthmatics.
STUDY DESIGN	Longitudinal study	Cross-sectional study	Longitudinal study
STUDY POPULATION	50 laboratory animal workers in four research centres. - Each subject was exposed to a minimum of two occasions per week for six months or longer. - There was no exclusion based on clinical history.	- Permanent (n = 139) and casual (n = 11) workers in a spice mill (total n = 150). - Mean employment duration of 6.9 years in the factory and 3.2 years in the current job.	165 subjects with asthma, measured at home, 82% of which were atopic, 18% of which were non-atopic. - Each subject was exposed to two visits, four years apart (mean = 47 months).
INTERVENTION/ EXPOSURE	Exposure to laboratory animals in the workplace.	Exposure to spices in the workplace.	Exposure to mite, dog and cat allergens in the household.
OUTCOME MEASURES	Symptom questionnaire, peak expiratory flow measurements, lung function and FeNO.	Immunological tests for common inhalants and occupational agents (garlic, chili pepper and wheat), spirometry and FeNO.	Lung function, FeNO, and immunological tests for sensitisation to mite, dog and cat allergens.
MEASUREMENTS	- Subjects were initially assessed on a Friday. - Subjects received instruction on the use of a peak flow meter and a symptom diary. - Having avoided contact with laboratory animals over the weekend, they were assessed at the beginning and at the end of each working day from Monday to Friday of the following week.	Serial FeNO measurements were conducted as follows: - Baseline pre-shift on Monday. - Post-eight-hour shift. - Pre-shift test on the following Tuesday.	Allergen exposure was measured using monoclonal ELISA. Each subject underwent two measurements, four years apart as follows: - All underwent spirometry and measurement of FeNO. - Allergic sensitisation was measured by skin-prick testing.
RESULTS	- Two of the 50 subjects had a positive specific IgE to one or more laboratory animal allergen (LAA). - Baseline FeNO were highest in two subjects sensitised to LAA, having FeNO of 213.0 ppb and 179.0 ppb. - Mean FeNO was (19.8 ± 20.1 ppb) and (21.7 ± 20.8 ppb) in the remaining seronegative symptomatic and non-symptomatic groups, respectively. - Progressive increases in FeNO occurred only in one of the seropositive individuals during the working week.	- The geometric mean of FeNO change across shift (15.43 ppb) was very similar to the mean change across the 24-hour period (15.84 ppb). - FeNO increase (>12%) across a 24-hour period was significantly associated (OR = 3.77; CI 1.01-14.24) with exposures to higher spice dust particulate but no effect observed across the eight-hour work shift.	There was a mean 1.5-fold decrease in FeNO over the 4-year period (p < 0.001).
LIMITATIONS	- Small sample size. - Subjects were not all asthmatic. - No mention made of important confounders. However, mention was made of the workplace protection not being uniform.	- No comparable unexposed group. - Short follow up duration	- The level of exposure was not measured at the second visit. - Possibilities for selection bias - No control group of healthy adults. - Possibility of important confounders (high doses of ICS among all participants).
CONCLUSION	Serial FeNO could assist in monitoring patients sensitised to occupational allergens. However, its value decreases if the patient is also sensitised and exposed to non-occupational allergens which can mask the FeNO changes.	FeNO level increase was more pronounced 24 hours after the exposure to spice-dust particulate.	Long-term exposure to dust mite and dog allergens in the home caused significant changes in bronchial hyperresponsiveness, but not necessarily in FeNO levels of asthmatic adults.

TABLE IIIB: CASE REPORTS OF ADULT WORKING POPULATIONS

AUTHORS	MERGET ET AL, 2014 ²²	MERGET ET AL, 2016 ²³
AIM OF STUDY	To assess the practicality of serial measurements of FeNO as diagnostic tool for occupational asthma.	A case report of triticale (wheat/rye) allergy in a farmer.
STUDY DESIGN	Case study	Case study
STUDY POPULATION	51-year-old male smoker working as a baker since adolescence who complained of shortness of breath and cough.	29-year-old farmer with hay fever and atopic dermatitis since adolescence diagnosed with work-related asthma.
INTERVENTION	Avoidance of exposure for two weeks.	Avoidance of exposure for two weeks.
OUTCOME MEASURES	Change of FeNO level over time.	Change of FeNO level over time.
MEASUREMENTS	FeNO measurement was performed once daily over a two-week holiday period and thereafter over three weeks of working days.	- FeNO measurement was performed once daily during a working week and thereafter over a two-week holiday period. - Measurements were done in the evenings, (after work) in the working period.
RESULTS	FeNO decreased to the normal level soon after the start of the holiday period and showed a clear increase after resuming work.	FeNO decreased gradually over time soon after the start of the holiday period.
LIMITATIONS	Case study design	Case study design
CONCLUSION	FeNO decreased over two weeks of allergen and irritants avoidance and showed a clear increase over the working-day period.	FeNO decreased over two weeks of allergen avoidance in a patient with occupational asthma to triticale.

aeroallergen has also been studied in asthmatic children. Piacentini et al⁷ studied the outcome of allergen avoidance at 1 756 m above sea level for three months in 20 asthmatic children who were sensitised to house-dust mite (HDM). FeNO levels decreased progressively in the first two weeks ($p = 0.014$) and remained unchanged for the next three months. This drop in FeNO was also reported by Peroni et al⁹ in HDM-sensitised asthmatic children living at high altitudes for nine months. The mean FeNO levels decreased by 50% in the first three months ($p = 0.030$); however, no further significant change was recorded over the remaining period. Huss-Marp et al have argued that avoidance of the allergen is not the only contributing factor in the decline of FeNO observed in these studies. This suggests that physiological changes at high altitude may also be a contributing factor.^{10,37} This study found that FeNO declined significantly in HDM-sensitised asthmatic children as a group and in the non-HDM-sensitised group or those with intrinsic asthma; however, no significant difference in the reduction between the two groups was observed. Karagiannidis et al³⁸ also reported a similar conclusion. It is, however, likely that there may have been residual exposure to HDM at this lower altitude compared to the Piacentini and Peroni studies that were done at higher altitudes. Furthermore, it is possible that by combining subjects who were sensitised to allergens other than HDM ($n = 251$) and those with intrinsic asthma ($n = 22$), this may have confounded the findings.

In an occupational context, Merget evaluated the effect of avoidance of exposure to inhalant allergens in two case studies: a farmer sensitised to triticale and a baker mildly sensitised to wheat and rye both demonstrated a decrease in FeNO after avoidance of the potential allergens for two weeks.^{23,39}

EXPOSURE TO SPECIFIC SENSITISING AGENTS

All the studies identified focused mainly on serial FeNO changes with exposure to high molecular weight (HMW) agents. However, it has been previously reported that the increase in FeNO after specific inhalation-challenge tests in patients with suspected occupational asthma is more strongly associated with exposure to HMW than to low molecular weight (LMW) agents, the former known to be commonly associated with allergic IgE-mediated airway inflammation.³¹

OTHER EXPOSURE CHARACTERISTICS

Finally, while it could be hypothesised that exposure duration, exposure concentration or cumulative exposure may play a role in determining serial changes of FeNO in population-based studies, we were unable to identify many studies that evaluated these potential relationships. However, Lemiere et al³¹ evaluated this association between serial changes in FeNO and the duration of exposure to the potential allergen during SIC tests and the association was found not to be significant ($OR = 0.99$, 95% CI 0.9–1.0). Although the overall association between the overall change in FeNO and the concentration of allergen exposure was not statistically significant, Van der Walt et al²⁵ found a significant association between workers exposed to high concentrations of spices and a >12% increase in FeNO in their mill workers ($OR = 3.77$, 95% CI 1.01–14.24). Furthermore, a positive correlation has also been demonstrated between the degree of FeNO reduction after HDM avoidance and baseline HDM allergen levels measured in the beds of subjects ($r = 0.618$, $p = 0.026$) by Piacentini et al in their study of asthmatic children.⁸

AIR POLLUTION

Exposure to air pollutants could contribute to changing

FeNO levels, especially in busy large cities. Adar et al¹⁷ found that reducing ultrafine particles by the adoption of clean-fuel technology in school buses led to a 16% reduction in FeNO among bus passengers. This association was more prominent in asthmatic children. Moreover, Holguin et al¹⁸ found that exposure to higher road traffic density was associated with a significant increase in FeNO in asthmatic children and a non-significant increase in healthy children. Furthermore, both studies found no association between FeNO and exposure to PM_{2.5} particulates. This suggests that PM_{2.5} may not be useful in studying the association between FeNO and air pollution in children.

HOST-ASSOCIATED FACTORS

ASTHMA EDUCATION TO IMPROVE ASTHMA CONTROL

The effect of asthma education programmes on asthma control has been evaluated through several studies of children. Kaminsky et al¹¹ evaluated 25 asthmatic children, 21 of them on inhaled corticosteroids (ICS), participating in a one-week camp organised with asthma education programmes. The overall mean FeNO dropped by 45% ($p < 0.001$) at the end of the week. This decline could be attributed to the increase in ICS compliance, which was found to reduce FeNO in asthmatics in a dose-dependent manner.^{40,41} However, three of the four children who were not on ICS also demonstrated a decrease in FeNO at the end of the camp. The authors indicate that it is also possible that the changes in FeNO could have been due to other additional factors such as allergen avoidance or absence of anxiety triggers in the home.^{42,43} Furthermore, Kaminsky et al did not specify the asthma control status of the subjects that were evaluated. It is possible that a large proportion were non-compliant or under-treated so that the change in FeNO could have been due to improved asthma control. This was evident in the study by Barreto et al,¹⁵ who studied asthmatic children with good asthma control in a sanatorium for one week, a study that was accompanied by an asthma education programme. The study reported that the mean baseline FeNO in asthmatics on ICS neither differed from that of the healthy subjects nor did it differ over the entire week. In contrast, asthmatics not on ICS had a higher FeNO baseline ($p < 0.005$) compared to the healthy subjects and showed a progressive decrease over the week until the difference reached non-significance ($p = 0.057$). This is further explained by the study of Jatakanon et al⁴⁴ that demonstrated a plateau of exhaled FeNO in response to higher doses of ICS.

Asthma education programmes have also been evaluated in adults in domestic and occupational settings. Dressel et al¹³ evaluated FeNO after a one-day asthma education programme in 81 animal farmers with occupational asthma who were sensitised to cow dander and storage mites. The overall mean FeNO decreased by 9% ($p = 0.042$) after 4–6 weeks after the programme and by 18% ($p = 0.003$) among those with a baseline FeNO of >35 ppb. The 43

subjects in this study were re-evaluated after one year to assess the long-term changes in FeNO after the asthma education programme.¹⁴ The mean FeNO decreased by 21% ($p = 0.001$) in the intervention group. While measures to reduce exposure to the allergens – such as the use of personal protective equipment, changing work clothes before going home and washing hair before going to bed – were major contributors to this reduction in FeNO in both studies, compliance with medication was also cited as an additional contributor to these positive findings. This was evident also in the study by Saito et al,¹² which provided an asthma education programme to 50 asthmatics with poor adherence to medication. The programme was aimed at increasing compliance with medications and at improving the inhalation technique. The study reported a significant decrease in the overall mean FeNO after a year of follow-up visits (at 3, 6 and 12 months from the baseline) in stable patients ($n = 42$), even though asthma medication was stepped down in 33% of the subjects. However, a non-significant reduction in FeNO was recorded in 16 subjects who were initially unstable and required an increase in ICS dosage or additional asthma medication during the course of the study.

ATOPY

It is well known that FeNO levels are higher among atopic subjects, irrespective of the domestic or occupational exposures.^{3–5} These findings were also reported by Van der Walt et al²⁵ in their study of spice-mill workers. However, strong associations between atopic status and longitudinal changes in FeNO have not been studied in detail. Changes in FeNO appear to be independent of atopic status.^{10,24} Spanier et al²⁰ found that the seasonal variation of FeNO did not differ between atopic and non-atopic subjects. Moreover, Lemiere et al³¹ reported a non-significant positive association between changes in FeNO and atopy status (OR 2.0, 95% CI 0.5–7.5) in their study of FeNO measured after SIC to occupational agents in patients with occupational asthma.

SMOKING STATUS

It is well known that smoking is associated with a decreased baseline FeNO in subjects.^{3–5} However, strong associations between smoking status and longitudinal changes in FeNO have not been studied in detail. Lemiere et al,³¹ in their study of patients with occupational asthma, found a non-significant positive association between FeNO changes and negative smoking status (OR 1.5, 95% CI 0.5–4.3) after SIC to occupational agents in patients with occupational asthma.

In children, passive smoking may have an effect on longitudinal changes in FeNO. Spanier et al²⁰ found that exposure to passive smoking measured by a nicotine dosimeter led to a significant decrease in FeNO. However, this association disappeared when the exposure reported by the parent's survey was used – suggesting possible recall bias.

BASELINE LUNG FUNCTION AND FeNO

Whereas the relationship between baseline FeNO and forced expiratory volume (FEV₁) has been evaluated in a number of studies, there are few studies evaluating the association between baseline FEV₁ and the longitudinal change in FeNO. Peroni et al⁹ did not find a correlation between FEV₁ and longitudinal changes in FeNO in their study. Lemiere et al³¹ also reported a non-significant association between changes in FeNO post-SIC and baseline FEV₁. This association was also not present with a maximum fall in FEV₁ after SIC. However, Saito et al¹² found a significant correlation between a change in FeNO and the change in FEV₁ in the first three months of their study. This change remained significant until the end of the study after 12 months of baseline.

While it could be hypothesised that baseline FeNO may be a good indicator of the magnitude of future change in serial FeNO, studies in this area that evaluated this potential relationship were scant. In children, Spanier et al²⁰ and Cutts et al²¹ found a significant association between

baseline FeNO and longitudinal changes in FeNO. However, Lemiere et al³¹ were unable to demonstrate an association between baseline FeNO (>25ppb) and a change in FeNO post-SIC in an adult group.

CONCLUSION

To conclude, FeNO can be regarded as an important marker of airway inflammation in asthma among both symptomatic and asymptomatic subjects. Whereas the predictors of baseline FeNO levels have been evaluated in several clinical and population-based studies, the evidence for various factors associated with longitudinal changes in FeNO need further investigation. These include smoking, atopy, baseline FeNO, baseline FEV₁ and exposure characteristics (agent and dose), which need further evaluation, especially in occupational settings.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

This article has been peer reviewed.

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Ethics CPD Questionnaire

PERINATAL ETHICS – IS THERE A CONFLICT

Ethics articles are accredited for ethics CPD points. Log in to the ALLSA website (www.allergysa.org) and click on “My CPD” to submit your answers. Kindly send submissions or suggestions for topics to the section editor, Prof Sharon Kling at sk@sun.ac.za. This CPD activity is for ALLSA members only.

INDICATE TRUE OR FALSE

1. *True or false:* A major moral objection to respecting the pregnant woman's autonomy is that this entitles her to terminate an unwanted pregnancy.
2. *True or false:* Another moral objection to respecting the pregnant woman's autonomy is that the foetus has the capacity to develop into a person.
3. *True or false:* The ethical dilemma in perinatal ethics is best described as a maternal-foetal conflict.
4. *True or false:* In perinatal ethics the pregnant woman's autonomy conflicts with distributive justice.
5. *True or false:* In perinatal ethical dilemmas, beneficence-based obligations to the foetus outweigh the autonomy of the pregnant woman.
6. *True or false:* The foetus has no legal rights until it is born.
7. *True or false:* Viability is an important consideration in the debate surrounding termination of pregnancy, and is usually regarded to be 26 weeks' gestation.
8. *True or false:* In the case where a pregnant woman refuses to undergo a caesarean section for foetal distress, it is appropriate for the medical team to approach the court to override her decision.
9. *True or false:* In the case where an HIV-positive pregnant woman refuses to take antiretroviral therapy (ART), it is appropriate for the medical team to approach the court to force her to take ART to protect the unborn foetus.
10. *True or false:* In the case where an HIV-positive woman refuses to take antiretroviral therapy (ART) and refuses to administer antiretrovirals (ARVs) to her new-born baby son, the medical team may approach the court to compel her to administer the ARVs to him.