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Less Air Pollution Leads to Rapid Reduction of Airway Inflammation and Improved Airway Function in Asthmatic Children

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What's Known on This Subject

Air pollution can promote airway inflammation and negatively affect lung function, posing significant health risks for children with chronic respiratory problems like asthma. However, it is unknown whether this process is reversible, so that limiting pollution will benefit these children.

What This Study Adds

This study provides the first objective evidence that limiting real-life exposure of allergic asthmatic children to outdoor air pollution is followed by measurable reduction in airway inflammation and improved airway function, implying that better air quality may rapidly lead to clinical improvement.

ABSTRACT

OBJECTIVE. Air pollution can promote airway inflammation, posing significant health risks for children with chronic respiratory problems. However, it is unknown whether this process is reversible, so that limiting pollution will benefit these children. We measured the short-term response of allergic asthmatic children exposed to a real-life reduction in outdoor air pollution by using noninvasive biomarkers of airway inflammation and function.

PATIENTS AND METHODS. Thirty-seven untreated allergic children with mild persistent asthma were recruited from a highly polluted urban environment and relocated to a less polluted rural environment. Air pollution, pollen counts, and meteorological conditions were carefully monitored at both sites. Nasal eosinophils, fractional exhaled nitric oxide, peak expiratory flow, and urinary leukotriene E₄ were measured first in the urban environment and then again 7 days after relocation to the rural environment.

RESULTS. One week after relocation to the rural environment, we measured, on average, a fourfold decrease in nasal eosinophils and significant decrease in fractional exhaled nitric oxide. We also noted an improvement in lower airway function, reflected by highly significant increase in peak expiratory flow. In contrast, mean urinary leukotriene E₄ concentration remained unchanged after 1 week of exposure to the rural environment.

CONCLUSIONS. Better air quality is associated with a rapid reduction of airway inflammation in allergic asthmatic children. Nasal eosinophils and fractional exhaled nitric oxide are sensitive indicators of this effect, and their rapid decline is paralleled by improved airway function measured by peak expiratory flow. Leukotriene synthesis has a more variable response to environmental modifications. *Pediatrics* 2009;123:1051–1058

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Drs Renzetti and Silvestre contributed equally to this work.

Key Words

allergy, eosinophils, exhaled nitric oxide, leukotrienes, peak expiratory flow, rhinitis

Abbreviations

PM₁₀—particulate matter <10 μm in diameter
CO—carbon monoxide
PEF—peak expiratory flow
cysLT—cysteinyl leukotriene
LTE₄—leukotriene E₄ concentration
ARTA—Regional Agency for Environmental Protection
NO₂—nitrogen dioxide

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IN RECENT DECADES, we have experienced a global increase in the prevalence of asthma and other allergic diseases, particularly among children living in the urban areas of economically developed countries. This has led to the hypothesis that environmental factors, especially indoor and outdoor air quality, play an important role in the inception of allergy and asthma early in life, and later trigger acute exacerbations of respiratory symptoms.^{1–3} Specifically, several studies have shown that exposure to particulate matter (PM₁₀) increases the use of asthma medications and the rate of hospital admissions for asthma.^{4–8} Ozone worsens airway inflammation and resistance in patients with asthma.^{9–11} Nitrogen oxides predispose to respiratory infections, wheezing exacerbations, and stronger response to inhaled allergens.¹² Carbon monoxide (CO)¹³ and benzene¹⁴ are strong independent risk factors for emergency department and hospital admissions of asthmatic children.

In light of the epidemiologic evidence outlined previously, and assuming that the inflammatory response of the airways to airborne irritants is reversible, it is reasonable to hypothesize that limiting outdoor air pollution will benefit airway inflammation, thereby improving the clinical and functional manifestations of asthma and other chronic respiratory disorders. However, little scientific evidence is available to support this hypothesis, and also it is not known how rapidly a favorable change in air quality can lead to measurable reduction in airway inflammation and to improvement in airway function. To address these questions, the present study sought to determine whether a 1-week exposure to a less polluted environment affects the expression of specific noninvasive biomarkers used to monitor airway inflammation and airflow limitation in allergic children with physician-diagnosed asthma.

Previous studies have shown that exposure to ozone increases the number of eosinophils in nasal secretions,¹⁵ and more recent work found that personal and ambient air pollution correlate with increased fractional exhaled nitric oxide (FE_{NO}) concentration from the lower airways of children with asthma.¹⁶ Therefore, we measured the response of these sensitive biomarkers of upper and lower airway inflammation to real life, carefully monitored environmental exposures to airborne pollutants and allergens, and explored the correlation between airway inflammation and function measured by peak expiratory flow (PEF). Furthermore, in light of the role played by cysteinyl leukotrienes (cysLTs) in the pathophysiology of allergic inflammation of the upper and lower airways,¹⁷ we measured the excretion of their terminal metabolite leukotriene E₄ (LTE₄) in the urine.

PATIENTS AND METHODS

Subjects

All subjects were recruited between June 1 and July 31, 2006, from the Asthma Clinic of the Department of Pediatrics of the Civil Hospital in Pescara, Italy. This study was approved by the local institutional review board, and informed consent was obtained from the parents of each subject.

We included children 7 years of age or older, with physician-diagnosed mild persistent asthma as defined by the Global Initiative for Asthma, positive skin-prick test for allergy to dust mites, who were able to perform PEF and FE_{NO} measurements. Exclusion criteria included symptoms or any medical treatment in the 3 weeks preceding relocation to the rural environment. Throughout the study, the children were closely monitored by medical and nursing staff but received no medications.

A total of 60 children were approached, but 16 could not be enrolled because their parents declined consent. Five subjects experienced respiratory symptoms before relocation, resumed therapy with inhaled corticosteroids and short-acting β -agonists, and withdrew from the study. During the study, we also excluded 1 child who developed fever and another who had problems performing reproducible PEF measurements.

All participating families implemented in their homes environmental control strategies for avoiding indoor allergens and pollutants, particularly dust mites by encasing pillows and mattresses in air-tight covers and washing bed linens and blankets weekly in hot water. All exposure and clinical measurements were performed first in the urban environment on the day before relocation (day 0), and then again 7 days after relocation to the rural environment (day 7).

Exposure Measurements

Urban Environment

A network of 6 fixed air quality monitoring stations operates continuously in the city of Pescara, Italy, under the Regional Agency for Environmental Protection (ARTA). These stations are located in densely populated urban areas and collect hourly data on PM₁₀, ozone, nitrous oxide (NO₂), CO, and benzene. These data were used to extrapolate the mean daily exposure to each pollutant during the week preceding relocation, and the mean of these daily values was used for our analysis. PM₁₀ levels were measured by B-ray atomic absorption, ozone by ultraviolet photometry, NO₂ by chemiluminescence, CO by infrared photometry, and benzene by gas chromatography. We also monitored local meteorological conditions at the same time points, and allergen levels were measured by using a portable volumetric sampler (VPPS 2000 [Lanzoni, Bologna, Italy]).¹⁸

Rural Environment

This part of the study was conducted during a school camp held in Ovindoli, Italy, a rural area located 1500 m above sea level with very low motor vehicle traffic. During the 7 days of the study, the children were housed in a hotel without their families and were supervised by members of the Department of Pediatrics' medical and nursing staff. Air quality was monitored from the parking lot of the hotel where the children were housed by a mobile station certified by ARTA to obtain measurements comparable with the urban data. These data were used to extrapolate the mean daily exposure to each pollutant during the week after relocation, and the mean of these daily values was used for our analysis. PM₁₀ levels were measured with an oscillating microbalance, ozone and NO₂ by differential optical absorption spectrometry, CO by infrared photometry, and benzene by gas chromatography. Meteorological conditions were monitored at the same time points, and allergen levels were measured by using the same VPPS air sampler used for the urban environment.

Clinical Measurements

Nasal Eosinophils

The mucosa was scraped with a plastic curette from the medium third of the inferior nasal turbinate on days 0 and 7 of the study period. The specimens were stained with the May-Grunwald-Giemsa method and were examined under microscope by a blinded investigator.

TABLE 1 Skin-Prick Allergy Tests

Allergen	No. Positive/ No. of Total Tests
Dust mites	37/37
Gramineae pollens	16/37
Oleaceae pollens	11/37
Urticaceae pollens	7/37
Cupressaceae pollens	1/37
Betullaceae pollens	1/37

Exhaled NO

The FE_{NO} concentration from the lower airways was measured with a handheld analyzer (Niox Mino [Aerocrine, New Providence, NJ])¹⁹ at 5 PM on days 0 and 7 of the study period using a methodology compliant with the current American Thoracic Society (ATS)/European Respiratory Society (ERS) international guidelines.^{20,21}

PEF

PEF was measured with a standard device at 8 AM, 3 PM, and 10 PM on days 0 and 7 of the study period. The mean of the 3 measurements was used for our analysis.

Urinary LTE₄

Urine samples were collected on days 0 and 7 of the study period and were analyzed in duplicate using a competitive enzyme-linked immunoassay (Cayman Chemical, Ann Arbor, MI), as described previously.²²

Statistical Analysis

Data are expressed as mean $\pm$ SEM, unless indicated otherwise. Exposure and clinical measurements obtained in the urban versus rural environment were compared by using the paired Student's *t* test, and Pearson's correlation coefficients were used to assess the relationship between inflammatory biomarkers and functional measures. Statistical analysis was performed by using StatView 5.0.1 software (SAS Institute, Cary, NC). Differences having a *P* value of $<.05$ were considered significant.

RESULTS

We studied 37 allergic children (25 males and 12 females; age: 9.9 ± 0.3 years) with physician-diagnosed mild persistent asthma. Seventy percent (26 of 37) of these children also had clinical diagnosis of allergic rhinitis, 16% (6 of 37) atopic dermatitis, and 5% (2 of 37) allergic conjunctivitis. Results of their skin-prick tests for common airborne allergens are summarized in Table 1. All subjects were allergic to dust mites. Of the tests for pollens, 43% were positive to *Gramineae*, 30% to *Oleaceae*, and 19% to *Urticaceae*, whereas positivity to *Cupressaceae* and *Betullaceae* was rare.

The rural environment was located 1500 m above the urban environment, which explains the lower atmospheric pressure ($P = .003$) and temperature ($P < .0001$), whereas humidity ($P = .84$) and wind speed ($P = .85$) were similar (Table 2). All of the pollutants tested

TABLE 2 Meteorological Conditions

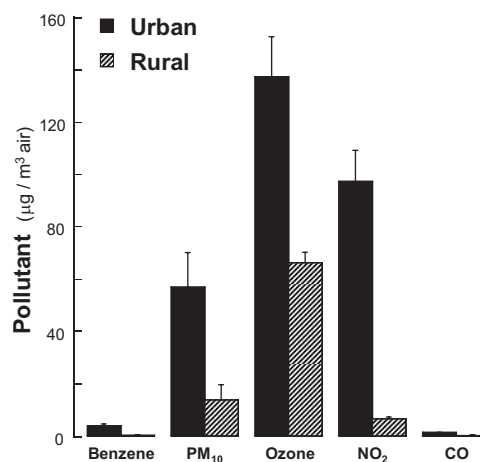
Variable	Urban, Mean $\pm$ SD	Rural, Mean $\pm$ SD	<i>P</i>
Temperature, °C	20.5 $\pm$ 1.5	12.8 $\pm$ 1.1	.0025
Humidity, %	74.7 $\pm$ 1.5	73.7 $\pm$ 1.4	.8417
Atmospheric pressure, millibar	1015 $\pm$ 10	863.2 $\pm$ 2.1	$<.0001$
Wind speed, m/s	0.62 $\pm$ 0.02	0.64 $\pm$ 0.32	.8494

TABLE 3 Exposure Measurements

Exposure	Urban, Mean $\pm$ SD, $\mu\text{g}/\text{m}^3$ of air	Rural, Mean $\pm$ SD, $\mu\text{g}/\text{m}^3$ of air	<i>P</i>
Benzene	3.9 $\pm$ 0.5	0.2 $\pm$ 0.1	.0001
PM ₁₀	56.9 $\pm$ 13.1	13.8 $\pm$ 5.6	.0003
Ozone	137.3 $\pm$ 15.3	66.2 $\pm$ 3.9	.0002
NO ₂	97.4 $\pm$ 11.8	6.6 $\pm$ 0.5	$<.0001$
CO	1.3 $\pm$ 0.1	0.2 $\pm$ 0.1	$<.0001$

(Table 3) were present at significantly lower concentrations in the rural environment compared with the urban environment ($P < .001$). The largest differences were measured in the concentrations of benzene and NO₂ that were, respectively, 20-fold and 15-fold lower in the rural environment (Fig 1), whereas relatively smaller differences were measured for CO (sevenfold), PM₁₀ (fourfold), and ozone (twofold). In contrast, the exposure to airborne allergens did not change significantly moving from the urban to the rural environment (Table 4), with the only exception of the *Fagaceae* pollen ($P < .01$) to which none of the study subjects was sensitized.

This environmental modification was rapidly followed by measurable changes in biomarkers of upper and lower airway inflammation. Specifically, we found an average fourfold decrease in nasal eosinophils ($P = .002$; Fig 2A and B). This effect was quite consistent, and eosinophils became virtually undetectable ($<1\%$) in the upper airways of most subjects after 1-week exposure to

**FIGURE 1**

Differences in the mean concentrations of airborne pollutants measured in the urban and rural environments compared in this study. All differences were found statistically significant, with $P < .001$.

TABLE 4 Pollen Counts

Pollen	Urban, Mean (SD), Pollen Grains per m ³ of Air	Rural, Mean (SD), Pollen Grains per m ³ of Air	P
<i>Aceraceae</i>	0	0	
<i>Betullaceae</i>	0	0	
<i>Cheno-Amarantaceae</i>	0	0.35 ± 0.56	.156
<i>Composite</i>	0.07 ± 0.17	0	.341
<i>Corylaceae</i>	0.07 ± 0.17	0	.341
<i>Cupressaceae</i>	0	0	
<i>Cyperaceae</i>	0	0	
<i>Euphorbiaceae</i>	0	0	
<i>Fagaceae</i>	0.07 ± 0.17	1.1 ± 0.4	<.01
<i>Gramineae</i>	0.21 ± 0.23	0.35 ± 0.67	.64
<i>Myrtaceae</i>	0	0	
<i>Oleaceae</i>	0.21 ± 0.35	0.77 ± 0.72	.119
<i>Pinaceae</i>	0.35 ± 0.67	0.42 ± 0.84	.877
<i>Plantaginaceae</i>	0	0	
<i>Platanaceae</i>	0	0	
<i>Polygonaceae</i>	0	0	
<i>Salicaceae</i>	0.14 ± 0.34	0.07 ± 0.17	.664
<i>Ulmaceae</i>	0	0	
<i>Urticaceae</i>	1.61 ± 1.49	0.35 ± 0.67	.088
<i>Alternaria</i>	0.28 ± 0.34	0.49 ± 0.67	.511
<i>Cladosporium</i>	1.05 ± 0.99	3.64 ± 5.53	.285
<i>Epicoccum</i>	0	0	
<i>Polytrincium</i>	0	0	

the rural environment. Living in a less polluted environment was also associated with reduced eosinophilic inflammation of the lower airways, reflected by a significant decrease in mean FE_{NO} concentration ($P = .028$; Fig 3A and B), and with consistent improvement in lower airways function reflected by a highly significant increase in mean PEF ($P < .0001$; Fig 4A and B).

Baseline FE_{NO} concentrations measured in the urban environment were normal (5–20 ppb) in 15 subjects, intermediate (20–35 ppb) in 10 subjects, and high (>35 ppb) in 12 subjects. Rural FE_{NO} concentrations were significantly lower in subjects with high urban FE_{NO} ($P = .002$), whereas no significant change was measured in children with intermediate ($P = .79$) or normal ($P = .86$) urban FE_{NO} (Fig 5A). Also, the change in PEF was not correlated with FE_{NO} concentration ($r = 0.18$; $P = .29$), and a similar increase in airway function was measured in all 3 FE_{NO} subgroups ($P < .001$; Fig 5B).

The leukotriene response to environmental change was rather variable, increasing or decreasing sharply in some subjects while changing little in most. As a result, we found no statistically significant change in the mean urinary LTE₄ concentration after 1-week exposure to the less polluted rural environment ($P = .974$; Fig 6, A and B). We were also unable to identify any specific factor predictive of the different patterns of leukotriene response in our subjects.

DISCUSSION

This study is the first adopting a real-life experimental approach to analyze the impact of outdoor air pollution on respiratory health in childhood. Its results suggest that lowering the exposure of allergic asthmatic children

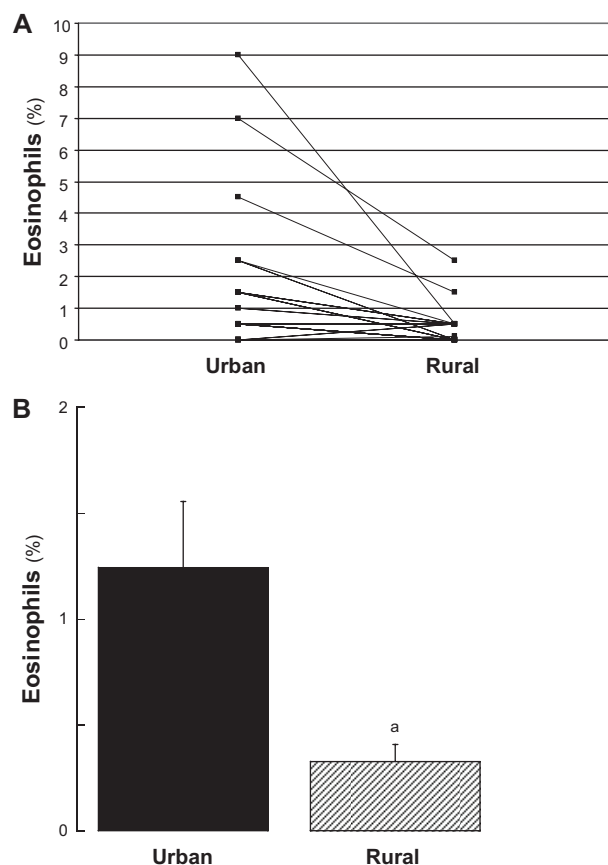


FIGURE 2 Eosinophils counted in nasal specimens collected before and 1 week after relocation from a more polluted urban environment to a less polluted rural environment. A, Paired dot plots showing change in individual patients. B, Comparison of mean ($\pm$ SEM) values. ^a $P < .01$.

to airborne pollutants is rapidly followed by measurable improvements in airway inflammation and function. Nasal eosinophils came out as the most sensitive biomarker to monitor pollution-induced airway inflammation, decreasing to virtually normal levels just 1 week after real-life relocation from a more polluted urban environment to a less polluted rural environment. Also the FE_{NO} concentration decreased significantly after relocation in children that had more active lower airway inflammation while living in a highly polluted urban environment.

Nasal eosinophils counts are primarily a marker of allergic inflammation of the upper airways,²³ whereas FE_{NO} has been shown to be closely related to the degree of eosinophilic inflammation and methacholine responsiveness of the lower airways.²⁴ These biomarkers are well-established direct indicators of inflammation, although their clinical relevance and degree of correlation with disease activity remain controversial. Although we elected not to obtain induced sputum to minimize discomfort for our young patients and because of its lower reliability in mild asthmatic children,^{25,26} FE_{NO} has been shown to correlate very well with the number of eosinophils in sputum.²⁴ As in several previous studies,^{26,27} we found no significant correlation between FE_{NO} and lung

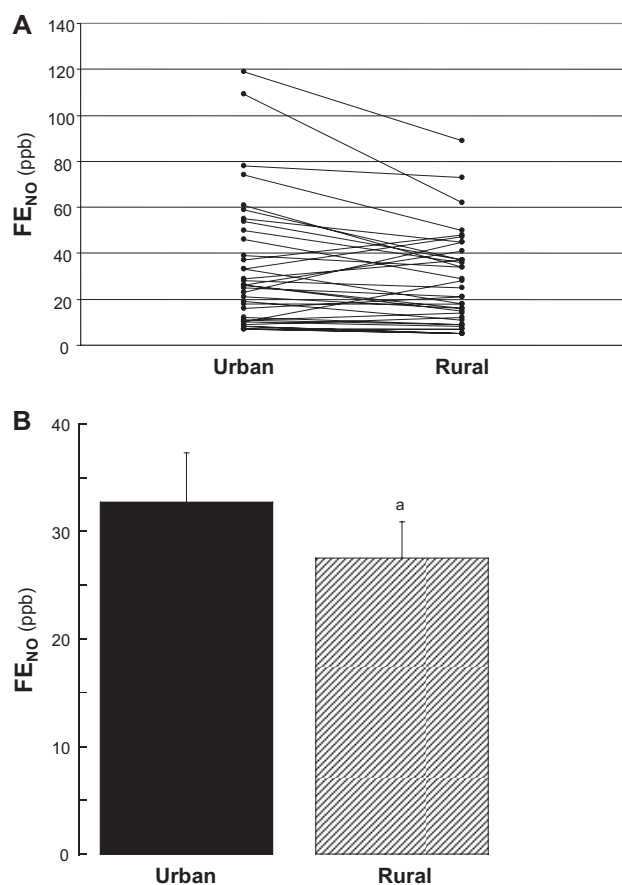


FIGURE 3

FE_{NO} concentration measured before and 1 week after relocation from a more polluted urban environment to a less polluted rural environment. A, Paired dot plots showing change in individual patients. B, Comparison of mean ($\pm$ SEM) values. ^a $P < .05$.

function measurements, suggesting that these tests reflect different pathophysiologic mechanisms of asthma.

Importantly, breathing cleaner air was associated in most children with a rapid and highly significant functional improvement in expiratory airflow. The subjects of this study were established patients of the asthma clinic and therefore they were quite experienced with the use of peak flow meters, which they were requested to use 2 to 3 times per week when clinically stable and 3 times per day during exacerbations. Therefore, it is extremely unlikely that improved performance may have contributed to the increase in PEF observed during the study.

We deliberately limited our study to children with mild persistent asthma and without therapy to avoid the possibility that antiinflammatory medications would mask environment-driven effects on inflammatory and functional biomarkers, and that our data would be confounded by variable adherence to therapy. On the other hand, recent studies in adults (28) suggest that the magnitude of the changes measured in our end points would be much larger in patients with more severe asthma and more compromised airway function. Also, some inflammatory and functional changes may lag several days behind the causative environmental modifications²⁹ and may therefore be missed in a short-term study, although

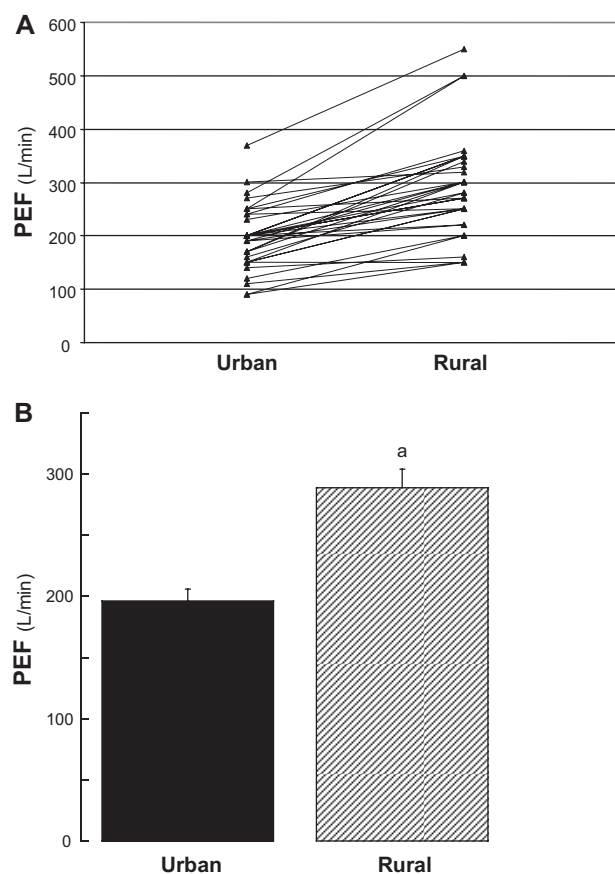


FIGURE 4

PEF measured before and 1 week after relocation from a more polluted urban environment to a less polluted rural environment. A, Paired dot plots showing change in individual patients. B, Comparison of mean ($\pm$ SEM) values. ^a $P < .001$.

again similar real-life studies have shown significant changes within hours from exposure.²⁸

All children included in this study met Global Initiative for Asthma criteria for the diagnosis of mild persistent asthma, and consistent with these guidelines they were treated with regular inhaled corticosteroid therapy, which was suspended at least 3 weeks before the study. The protocols adopted by the asthma clinic where these children were recruited prescribe a 6-month cycle of inhaled corticosteroid therapy after the diagnosis of mild persistent asthma. If the patient is clinically stable after this cycle, controller therapy is suspended and it is resumed in combination with a rescue short-acting β -agonist only if symptoms recur. Although management guidelines recommend the continued use of inhaled corticosteroids for patients with mild persistent asthma, recent studies indicate that these patients may not require regular treatment. Rather, the symptom-driven use of inhaled corticosteroids would be as effective as its regular use and would allow the use of lower cumulative doses.^{30,31}

Therefore, we feel that the management of our subjects was appropriate and based on sound scientific evidence, although it may have not adhered strictly to the adopted guidelines.

Our results are consistent with recent studies showing

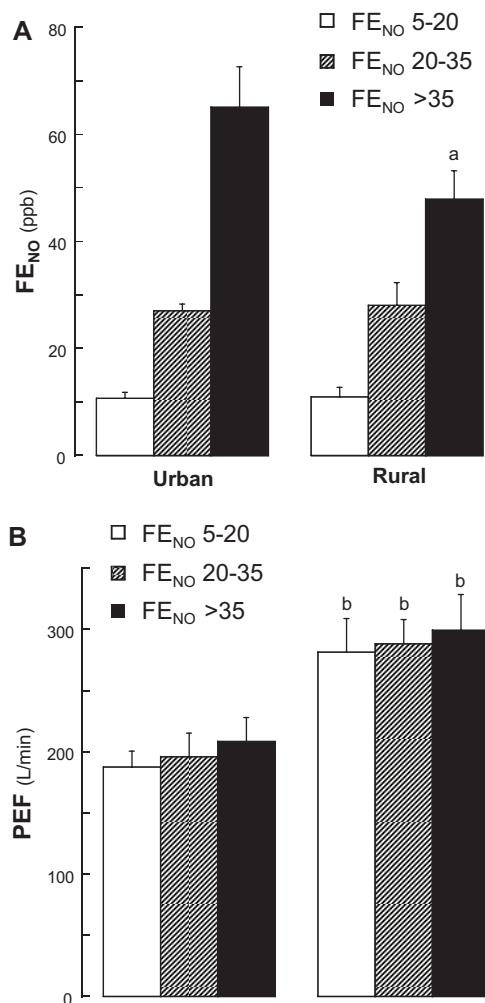


FIGURE 5

Comparison of inflammatory and functional changes after stratification of the study population on the basis of baseline urban FE_{NO} concentrations. A, FE_{NO}. B, PEF (mean ± SEM). ^a $P < .01$; ^b $P < .001$.

that traffic-related exposures are associated with increased airway inflammation and reduced lung function in children with asthma,³² and contribute the notion that this negative influence may be rapidly reversible. Another study conducted in Atlanta during the 1996 Summer Olympic Games concluded that decreased air pollution resulting from the implementation of alternative transportation strategies coincided with a transient reduction of asthma morbidity in children.³³ Collectively, these investigations underscore the impact of outdoor air pollution on allergic airways during childhood, whereas in the past more emphasis was placed on indoor pollution because of the fact that average children spend most of their time indoors. However, it is now recognized that outdoor air pollutants, particularly ozone and fine particles, can penetrate the building shell and enter the indoor environment,³⁴⁻³⁷ which provides another key to explain our findings. The reversible nature of pollution-induced airway inflammation emphasizes the importance of air quality for patients with asthma and allergic rhinitis, and suggests that pharmacological interventions

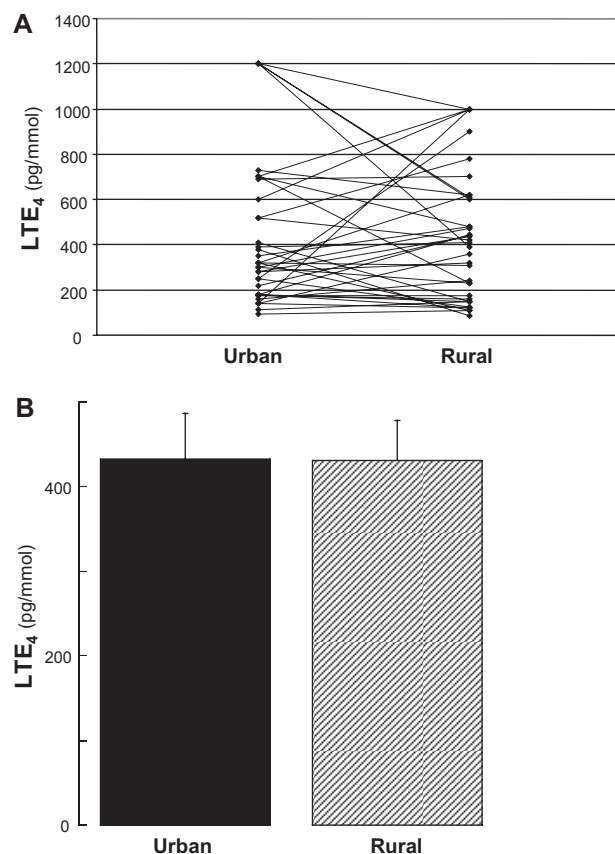


FIGURE 6

LTE₄ measured in urine samples collected before and 1 week after relocation from a more polluted urban environment to a less polluted rural environment. A, Paired dot plots showing change in individual patients. B, Comparison of mean (± SEM) values.

could be minimized or abolished when allergic asthmatic children live in a cleaner environment.

The impact of air pollution on asthma morbidity in children is of particular concern in Italy and other European countries. In recent years the concentration of some pollutants like CO, sulfur dioxide, and benzene has declined significantly in most European cities because of the improved efficiency of engines and fuels. However, differently from the declining national trends reported by the US Environmental Protection Agency, the concentrations of ozone, NO₂, and especially PM₁₀ remain high in most urban areas of both northern and southern Europe, rising frequently above the safety thresholds mandated by the European Union. Despite the improvement in air quality achieved in the United States by the pollution control programs instituted under the Clean Air Act, air pollution problems continue in many parts of the country and compel the development of new strategies to reduce emissions further.

Our findings cannot be explained by different patterns of allergic stimulation, as the only significant difference was an increase of *Fagaceae* pollens in the rural environment without correspondent sensitization. Also unlikely is a role of the indoor environment, because these children lived in families educated by the asthma clinic staff and their home environment was highly con-

trolled with strategies for avoiding exposures to common allergens and pollutants, particularly dust mites. Such level of indoor environmental control would be logistically impossible in a hotel, and therefore if the indoor influences were predominant we should have observed worse airway inflammation and function in the rural area, rather than the actual improvement we measured.

Surprisingly, the improvement in airway inflammation and function observed after relocation to the rural environment was not reflected by predictable changes in the urinary concentration of LTE₄, which is the end-product of cysLTs metabolism in activated mast cells, eosinophils, and monocytes.^{38–40} The lack of a consistent response to environmental modulation suggests that the production of cysLTs is strictly controlled by mechanisms intrinsic to the pathophysiology of allergic inflammation, or alternatively that this pathway has a slower response to extrinsic environmental changes.

Of course, there are some limitations to our study, largely deriving from the approach we and others²⁸ have adopted to mimic real life as close as possible and avoid the many artifacts inherent to the use of exposure chambers. In particular, it is impossible to rule out a potentially beneficial contribution of psychogenic factors associated with the change in environment. However, this interaction is less likely because, for most of the children involved in our study, the school camp coincided with their first experience away from home and their parents; therefore, more likely to increase rather than decrease stress. Furthermore, previous studies on the effect of psychological stress in asthmatic children failed to show significant changes in lung function,⁴¹ whereas our study shows a clear improvement in expiratory airflow.

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MERCK SEEKS GARDASIL'S APPROVAL FOR MALES

“Merck & Co. asked federal regulators to approve the use of its Gardasil human papillomavirus vaccine by boys and young men, potentially greatly expanding the market for the drug. The Whitehouse Station, NJ, drug maker asked the Food and Drug Administration to approve Gardasil's use in males aged 9 to 26 years old, for the prevention of genital warts and other lesions. In 2006, the FDA approved giving the human papillomavirus to girls and women of those ages. The request will likely renew public debate about the cost-effectiveness of Gardasil, which carries a price of \$360 for a three-dose regimen. A Merck spokeswoman said studies showed the vaccine proved effective in boys and young men.”

Rockoff JD. *Wall Street Journal*. January 6, 2009

Noted by JFL, MD

Less Air Pollution Leads to Rapid Reduction of Airway Inflammation and Improved Airway Function in Asthmatic Children

Gabriele Renzetti, Gaetano Silvestre, Claudio D'Amario, Egidio Bottini, Fulvia Gloria-Bottini, Nunzio Bottini, Alexander Auais, Miriam K. Perez and Giovanni Piedimonte

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