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Exhaled nitric oxide: The missing link between asthma and obesity?

To the Editor:

Asthma and obesity affect millions of persons worldwide. Both cross-sectional and longitudinal cohort studies have shown a positive association between both entities in children¹ and adults.² However, a pathophysiologic explanation for this association has not yet been established. We hypothesized that obesity might result in upregulation of pulmonary inflammatory mechanisms and studied the relationship between body mass index (BMI) and nitric oxide in exhaled air (eNO), which is an important inflammatory marker in patients with atopic asthma.³

We studied 24 (10 male and 14 female) healthy nonsmoking subjects. Subjects with a history of allergic rhinitis or lower respiratory complaints more severe than common colds were not included. After informed consent, eNO was measured during a 10-second expiration at 50 mL/s according to the American Thoracic Society guidelines (Niox; Aerocrine AB, Solna, Sweden).³ eNO values are reported as the mean value of 6 repeated measurements. None of the subjects took medications or nitrate-rich foods before the eNO measurements. The following lung function tests were performed (Masterlab, Viasys Healthcare, Hochberg, Germany): forced vital capacity, FEV₁, maximal expiratory volumes at 50% and 25% of total lung capacity, total lung capacity, residual volume, and carbon monoxide diffusion capacity corrected for alveolar volume and hemoglobin levels.

Mean (SD) age of the subjects was 27.9 (5.4) years, mean (SD) BMI was 23.0 (2.6) kg/m², and mean (SD) eNO level was 18.1 (7.4) ppb. Lung function parameters of all subjects were within the normal range. None of the

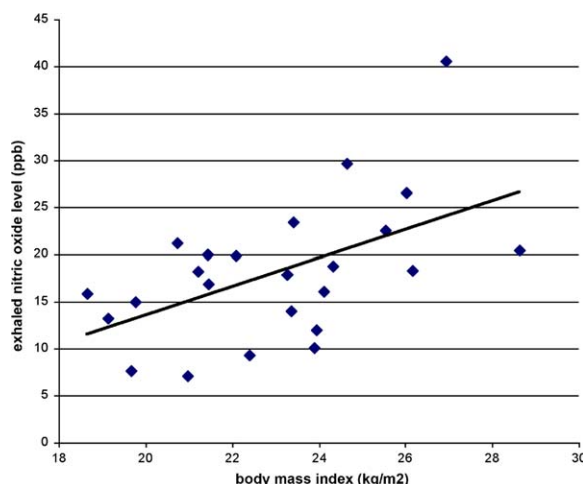


FIG 1. Association between BMI and eNO level in 24 healthy volunteers.

subjects had airflow obstruction, and mean (SD) FEV₁/forced vital capacity was 85.0% (6.2%). BMI was positively associated with mean eNO (linear regression coefficient, 1.5 ppb/kg/m²; 95% CI, 0.5-2.6; *P* = .007; Fig 1). This association did not change after adjustment for sex and age (1.5 ppb/kg/m²; 95% CI, 0.2-2.7; *P* = .02). No significant relationships between BMI or eNO and any of the lung function parameters were observed. The association between BMI and eNO was not influenced by adjustment for FEV₁ (1.8 ppb/kg/m²; 95% CI, 0.6-3.0; *P* = .005). Exclusion of the subject with the highest eNO value (Fig 1) did not materially influence the results.

Recent studies have shown that obesity leads to an increased release of proinflammatory molecules that contribute to obesity-associated complications. In obese subjects macrophage numbers in adipose tissue increase, producing significant amounts of TNF- α , inducible nitric oxide synthase, and IL-6.⁴ These data are supported by the finding that leptin, the protein of the putative obesity gene, upregulates the inflammatory immune response.⁵ Until now, no data on enhancement of inflammatory responses in the airways of obese subjects were available.

eNO has been established as a specific inflammatory marker in children and adults with atopic asthma. This marker in patients with asthma is strongly increased in comparison with healthy control subjects.³

Our findings show a significant increase in eNO levels in subjects with a high BMI. None of the subjects had a history or current symptoms of asthma or atopic disease. Lung function parameters were not negatively affected by increasing BMI. These data suggest direct or indirect upregulation of inflammatory processes outside the adipose tissue and suggest a contribution of obesity-related inflammatory activity to the pathophysiology of asthma. Linkage between obesity genes and nitric oxide synthase genes might be another explanation. Although our data from healthy subjects do not justify conclusions about pathophysiologic processes in disease states, our findings

highly suggest a linking role between asthma and obesity. Future studies should further elucidate the effects of obesity on the inflammatory system both inside and outside the adipose tissue.

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Wildfire smoke and respiratory symptoms in patients with chronic obstructive pulmonary disease

To the Editor:

Short-term increases in concentrations of particulate air pollution are associated with increased morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD).¹⁻³ Although most particulate air pollution is attributable to vehicular and industrial sources, biomass combustion during wildfires has been shown to have significant effects on outdoor air quality⁴ and climate as a result of generation of fine particulate matter. Although the relationship of domestic biomass fuel combustion with COPD has been described,⁵ the acute effect of wildfire smoke-related air pollution on patients with established COPD has not been well studied. Recent reports suggest that wildfire smoke exposure leads to increased health care utilization by subjects with asthma,⁶ raising the possibility that patients with COPD are similarly affected.

Air pollution events caused by wildfires can serve as natural experiments to test the hypothesis that short-term increases in air pollution concentrations have adverse

health effects. On June 8, 2002, a large wildfire known as the Hayman fire began southwest of Denver and was not controlled until July 18, 2002, ultimately burning 137,760 acres. On at least 2 days during this period, a plume of smoke and ash was carried over the Denver metropolitan area by prevailing winds (Fig 1). We prospectively evaluated the effects of this wildfire on air pollution and respiratory symptoms in adult subjects with COPD.

All research was approved by the National Jewish Medical and Research Center Institutional Review Board, and all subjects provided written informed consent. We recruited 21 Denver residents with COPD. Subjects were identified through previous participation in a panel study of air quality and respiratory symptoms in subjects with COPD. Eligibility criteria were as follows: (1) age ≥ 40 years, (2) >10 pack-year history of tobacco use, (3) airflow limitation as manifested by a $FEV_1 < 70\%$ of predicted and FEV_1 :forced vital capacity (FVC) ratio of $<60\%$, and (4) diffusing capacity for carbon monoxide $<70\%$ of predicted.

Between June 8, 2002, and June 29, 2002, subjects completed a daily telephone interview in which they reported 12-hour change in 5 symptoms: dyspnea, cough, chest tightness, wheezing, and sputum production. Change in symptoms was recorded on a 7-point scale on which symptoms over the last 12 hours were rated relative to the subject's baseline. Baseline symptoms were assigned a score of 4, with a score of 20 reflecting baseline severity of all 5 symptoms. A 1-point increase in any 1 symptom reflected worsening to slightly greater than usual, and a 2-point increase reflected worsening to much greater than usual. Over this same time frame, measurements of particulate matter (PM) with an aerodynamic diameter $<10 \mu\text{m}$ (PM_{10} , $\mu\text{g}/\text{m}^3$) and $<2.5 \mu\text{m}$ ($PM_{2.5}$, $\mu\text{g}/\text{m}^3$) and carbon monoxide (CO, ppm) were obtained from an air quality monitoring station located in Denver and operated by the Air Pollution Control Division of the Colorado Department of Public Health and Environment.

Evaluation of $PM_{2.5}$ concentrations revealed that there were significantly increased concentrations of particulate matter on 2 separate days; these were termed *spike days*. Concentrations of $PM_{2.5}$, PM_{10} , and CO on spike days were averaged and compared with mean concentrations on nonspike days (Wilcoxon rank-sum test). Median symptom scores on spike days were compared with median symptom scores on nonspike days using a repeated measurements ANOVA (SAS macro GLIMMIX) that accounted for the correlated nature of individual symptom. Analyses were performed using SAS (version 8.2; SAS Institute, Cary, NC).

Mean ($\pm$ SEM) age was 69.4 years $\pm$ 9.1 years, and 38.1% of subjects were female. Mean FEV_1 :FVC ratio was $53\% \pm 21\%$, with a group mean FEV_1 (L) of 1.6 ± 1.1 and FVC (L) of 2.8 ± 1.1 . Supplemental oxygen was used by 13 of 21 subjects (61.9%). Increased concentrations of $PM_{2.5}$, PM_{10} , and CO were observed on June 9, 2002, and June 18, 2002 (spike days 1 and 2). Concentrations of $PM_{2.5}$, PM_{10} , and CO on both spike days were