

Association between exhaled nitric oxide and systemic inflammatory markers

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Background: Asthma is an inflammatory condition of the airways, and there is some evidence to suggest that it is associated with a systemic inflammatory response, as measured by C-reactive protein (CRP) and fibrinogen. Exhaled nitric oxide is a noninvasive measure of asthmatic airway inflammation.

Objective: To determine if there is an association between exhaled nitric oxide and these systemic inflammatory markers.

Methods: The Dunedin Multidisciplinary Health and Development Study is a birth cohort of approximately 1,000 individuals born between April 1, 1972, and March 31, 1973. At the age of 32 years, study members were assessed for diagnosis of asthma, atopy by skin prick testing, smoking, body mass index, exhaled nitric oxide, high-sensitivity serum CRP, and plasma fibrinogen level.

Results: There was no significant association between exhaled nitric oxide and CRP ($P = .99$). There was a trend to an inverse association between exhaled nitric oxide and fibrinogen ($P = .049$), but this was not significant after adjusting for smoking and use of corticosteroids or after further adjustment for body mass index and atopy ($P = .71$).

Conclusion: In this population-based sample of young adults, there was no association between airway inflammation, as measured by exhaled nitric oxide, and systemic inflammation, as measured by either CRP or fibrinogen.

Ann Allergy Asthma Immunol. 2007;99:534–539.

INTRODUCTION

Asthma is a chronic inflammatory condition most commonly characterized by increased airway eosinophils, T lymphocytes, and mast cells¹ and is mediated by a complex array of cytokines.² In addition to airway pathology, there is evidence that asthma may be associated with a systemic inflammatory response. Olafsdottir et al³ reported an association between serum C-reactive protein (CRP) level and asthma in the European Community Respiratory Health Survey, and Jousilahti et al⁴ found an association between both CRP and fibrinogen levels and asthma in a cross-sectional study of Finnish men. Furthermore, airway hyperresponsiveness, one of the hallmarks of asthma,⁵ has also been associated with CRP, especially in women,⁶ and although there are fewer data

on fibrinogen, it may be associated with a deterioration in lung function in young adults.⁷

Although there is some evidence that systemic inflammation may be associated with a diagnosis of asthma, few studies have investigated if this reflects the extent of airway inflammation. Recently, Takemura et al⁸ reported that sputum eosinophilia was correlated with CRP, but this association was only found in a small group of corticosteroid-naïve asthmatic patients. The paucity of data on the association between airway and systemic inflammation may in part be because of the difficulties in undertaking sputum induction or bronchoalveolar lavage in large numbers of people. In contrast, the measurement of fractional exhaled nitric oxide (Fe_{NO}) is noninvasive and easy to perform. It correlates with the degree of sputum eosinophilia^{9,10} and has been useful in the diagnosis of asthma.^{11,12}

An association between airway and systemic inflammation could help to explain the widely recognized, but poorly understood, relationship between asthma and obesity.^{13,14} Obesity is regarded as a condition of low-grade systemic inflammation, with increased levels of CRP¹⁵ and fibrinogen.¹⁶ Furthermore, a correlation between body mass index (BMI) and Fe_{NO} has been reported in healthy adults but not in asthmatic patients.^{17,18} Interpretation of these findings is limited by the small sample sizes of these studies and because analyses combined results for men and women, who differ in body fat composition and may also have different Fe_{NO} levels.¹⁹

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Authors have nothing to disclose.

The Dunedin Multidisciplinary Health and Development Research Unit is funded by the Health Research Council of New Zealand; this study was supported by the Tony Hocken Scholarship, awarded by the Department of Medical and Surgical Sciences, Dunedin School of Medicine (Dr Sutherland).

Received for publication May 9, 2007.

Received in revised form June 4, 2007.

Accepted for publication June 11, 2007.

We investigated the association among FE_{NO} , CRP, and fibrinogen in a population-based birth cohort of approximately 1,000 men and women observed to the age of 32 years. We hypothesized that high levels of FE_{NO} would be associated with increased markers of systemic inflammation.

METHODS

Study Members

The Dunedin Multidisciplinary Health and Development Study is a longitudinal investigation of health and behavior in a population-based birth cohort.^{20–22} Study members were born in Dunedin, New Zealand, between April 1, 1972, and March 31, 1973. A total of 1,037 children (91.0% of eligible births, 51.6% male) participated in the first follow-up at 3 years, which constituted the base sample for the remainder of the study. The cohort represented the full range of socioeconomic status in New Zealand's South Island and is mostly of New Zealand European ethnicity. Of 1,015 living study members, 972 (95.8%) participated in the evaluation at the age of 32 years. The study was approved by the Otago Ethics Committee. Written informed consent was obtained from each study member.

Measurements

Study members answered questions from the European Community Respiratory Health Study²³ and the American Thoracic Society questionnaire.²⁴ Current asthma was defined as a self-reported diagnosis of asthma with symptoms within the past 12 months. Current smoking was defined as smoking at least 1 cigarette a day for a month in the previous year. Skin prick testing included testing for house dust mite, rye grass, cat, dog, horse, wool, *Aspergillus fumigatus*, *Penicillium*, *Cladosporium*, *Alternaria*, kapok, and cockroach (ALK Allergens, Allergy Canada, Thornhill, Ontario). A mean of the greatest width and length of the wheal was taken: 2 mm greater than the saline control was considered positive. Atopy was defined as a positive response to 1 or more allergens.

Fractional exhaled nitric oxide levels were measured on an analyzer (Logan LR2000 chemiluminescence analyzer; Logan Research Ltd, Rochester, England), using recommended protocols at a flow rate of 50 mL/s.¹⁹ Plateau FE_{NO} levels were read from the exhalation curves, and mean values from 2 acceptable exhalations were used. Tests on the first 44 study members were performed at a flow rate of 250 mL/s and were converted to 50 mL/s using a locally formulated and validated conversion factor.²⁵

High-sensitivity CRP was measured in serum using a particle-enhanced immunoturbidimetric analyzer (Hitachi 917; Roche Diagnostics, GmbH, Mannheim, Germany). Fibrinogen was measured using a fully automated cap-piercing coagulation analyzer (Sysmex CA1500; Mahberg, Germany).

Height and weight were measured in light clothing without shoes to calculate BMI.

Statistical Analysis

Levels of FE_{NO} , CRP, and fibrinogen were log transformed to natural logarithms to approximate normal distributions. Associations were analyzed by linear regression using $\log FE_{NO}$ as the dependent variable and $\log CRP$ and $\log$ fibrinogen as the independent variables. All analyses were adjusted for sex. The residuals were visually inspected to ensure that they were approximately normally distributed and that they were randomly scattered vs fitted values. Analyses were repeated with further adjustment for asthma diagnosis, smoking, use of inhaled or oral corticosteroids, atopy, and BMI. Further analyses tested for sex $\times$ $\log CRP$ and sex $\times$ $\log$ fibrinogen interactions and were also performed for men and women separately because each had different mean levels of FE_{NO} , CRP, and fibrinogen, and because the association between asthma and BMI may be different between sexes.²¹ Because of a previous report³ that found an association between CRP and asthma only in those who were nonallergic, analyses also tested for interactions between atopic asthma status and $\log CRP$ or $\log$ fibrinogen. Pregnant women ($n = 31$) were excluded from all analyses. Analyses were performed using the statistics package Stata 9.1 (Stata Corp, College Station, Texas).

RESULTS

A total of 896 nonpregnant study members provided readings for analysis of FE_{NO} , 862 for CRP, and 864 for fibrinogen. A total of 842 had FE_{NO} and CRP results and 843 had FE_{NO} and fibrinogen results.

FE_{NO} Levels

There was a significant difference in FE_{NO} levels between the sexes, with men having a higher mean level than women ($P < .001$) (Table 1). In both sexes, FE_{NO} levels were significantly higher in those with asthma and were also higher in those who were atopic. Current smokers had lower mean FE_{NO} levels than nonsmokers.

CRP and Fibrinogen Levels

Women had higher levels of both CRP and fibrinogen than men ($P < .001$) (Table 1). There were no significant differences for either sex between asthmatic and nonasthmatic, or between atopic and nonatopic, study members in either sex. Male smokers had a higher mean fibrinogen level than nonsmokers, but otherwise there were no significant differences in mean CRP or fibrinogen level in smokers compared with nonsmokers.

Associations Among FE_{NO} , CRP Level, and Fibrinogen Level

There was no significant association between FE_{NO} and CRP (Table 2). This remained the case after adjustment for smoking, corticosteroid therapy, atopy, and BMI. There was no significant interaction between sex and $\log CRP$ in the prediction of FE_{NO} ($P = .42$) and no significant associations were found when men and women were analyzed separately. There were no interactions between atopic status and $\log CRP$ in the

Table 1. Mean F_{ENO}, CRP, and Fibrinogen Values in Asthmatic, Atopic, and Smoking Subgroups

Variable ^a	Women		Men	
	Total No.	Geometric mean (95% confidence interval)	Total No.	Geometric mean (95% confidence interval)
F_{ENO} (n = 896)				
All values	425	11.6 (11.0–12.4)	471	15.3 (14.3–16.3)
Asthma				
Yes ^b	70	14.9 (12.4–18.0)	87	20.6 (17.3–24.6)
No	355	11.1 (10.4–11.8)	384	14.3 (13.4–15.3)
Atopy				
Yes ^b	243	13.8 (12.7–15.0)	291	18.1 (16.6–19.8)
No	181	9.3 (8.6–10.0)	175	11.7 (10.7–12.7)
Smoker				
Yes ^b	145	8.5 (7.7–9.4)	175	10.0 (9.1–11.0)
No	280	13.7 (12.8–14.7)	296	19.7 (18.3–21.2)
CRP Level (n = 862)				
All values	407	1.43 (1.27–1.60)	455	1.09 (0.99–1.20)
Asthma				
Yes	64	1.80 (1.35–2.40)	87	1.01 (0.81–1.25)
No	343	1.37 (1.20–1.55)	368	1.11 (0.99–1.24)
Atopy				
Yes	227	1.50 (1.29–1.76)	278	1.07 (0.95–1.21)
No	177	1.29 (1.08–1.55)	172	1.09 (0.92–1.28)
Smoker				
Yes	136	1.26 (1.04–1.53)	167	1.21 (1.04–1.41)
No	271	1.52 (1.31–1.76)	288	1.02 (0.90–1.16)
Fibrinogen Level (n = 864)				
All values	408	264 (259–270)	456	242 (238–247)
Asthma				
Yes	64	271 (255–288)	87	245 (235–255)
No	344	263 (257–269)	369	242 (237–247)
Atopy				
Yes	227	262 (255–270)	278	240 (234–246)
No	178	265 (257–274)	173	246 (239–254)
Smoker				
Yes	137	267 (257–277)	168	251 (244–258) ^c
No	271	263 (256–270)	288	237 (231–243)

Abbreviations: CRP, C-reactive protein; F_{ENO}, fractional exhaled nitric oxide.

^a For F_{ENO}, data are given as parts per billion; for CRP level, data are given as milligrams per liter; and for fibrinogen level, data are given as milligrams per deciliter.

^b Differences in F_{ENO} between asthmatic and nonasthmatic, between atopic and nonatopic, and between smoking and nonsmoking study members were significant in both sexes ($P < .001$).

^c The difference in fibrinogen level by smoking status was significant in men ($P = .005$).

prediction of F_{ENO} whether the sexes were analyzed together ($P = .89$) or separately (women, $P = .12$; and men, $P = .25$).

There was an inverse association between F_{ENO} and fibrinogen in the sex-adjusted linear regression model, which was of borderline statistical significance. This was no longer significant after adjusting for smoking, corticosteroid therapy, atopy, and BMI (Table 2). There was no significant interaction between sex and logfibrinogen in the prediction of F_{ENO} ($P = .73$) and no significant associations between F_{ENO} and fibrinogen in men or women. There were no interactions between atopic status and logfibrinogen in the prediction of

F_{ENO} whether the sexes were analyzed together ($P = .87$) or separately (women, $P = .71$; and men, $P = .63$).

DISCUSSION

We found no evidence that asthmatic airway inflammation measured by F_{ENO} was associated with increased levels of the nonspecific systemic inflammatory marker CRP or fibrinogen. For CRP, there were no significant associations with F_{ENO} in any of the analyses. For fibrinogen, there was a trend to an overall inverse association between F_{ENO} and fibrinogen, suggesting that systemic inflammation was associated

Table 2. Association Among FE_{NO} , CRP, and Fibrinogen^a

Variable	LogCRP			Logfibrinogen		
	Total No.	Coefficient	P value	Total No.	Coefficient	P value
Adjusted for sex	842	−0.001	.99	843	−0.220	.049
Female	396	0.015	.57	397	−0.260	.08
Male	446	−0.018	.58	446	−0.182	.27
Adjusted for sex, smoking, and corticosteroid use ^b	842	−0.001	.97	843	−0.100	.33
Adjusted for sex, smoking, corticosteroid use, atopy, and BMI ^b	837	0.021	.30	837	0.039	.71

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FE_{NO} , fractional exhaled nitric oxide.

^a Analysis by multiple linear regression, first adjusted for sex, then also adjusted for smoking, any corticosteroid use, atopy, and BMI, using log FE_{NO} as the dependent variable and either logCRP or logfibrinogen as the independent variable.

^b Inhaled corticosteroid therapy (n = 54) and oral corticosteroid therapy (n = 1) were used.

with reduced airway inflammation. This was in the opposite direction than had been predicted and was no longer significant after adjusting for smoking and corticosteroid therapy.

Our findings seem to contrast with other studies investigating systemic inflammation and asthma. Jousilahti et al⁴ found a positive association among CRP level, fibrinogen level, and asthma diagnosis in a cohort of more than 1,500 Finnish men, and Olafsdottir et al³ found an association between CRP and nonallergic asthma in the European Community Respiratory Health Survey. However, there are some differences between these studies and ours. The Finnish men were older (aged 45–74 years), and it is possible that some of the asthma diagnoses were chronic obstructive pulmonary disease, given the high rate of current or previous smoking. If so, this could confound the association, given that chronic obstructive pulmonary disease has been associated with increased levels of CRP²⁶ and fibrinogen.²⁷ The study by Olafsdottir et al also covered a range of ages (mean, approximately 42 years), whereas all our participants were within a year of their 32nd birthday. Furthermore, 45% of the asthmatic patients in the European Community Respiratory Health Survey were classified as nonallergic by specific serum IgE test results, whereas only 16% of the Dunedin study asthmatic patients were nonatopic on skin prick test results, which suggests a lower rate of “nonallergic” asthma. We did not, however, find any significant interactions between atopic status and either CRP or fibrinogen level in the regression analyses, indicating that the association between these systemic inflammatory markers and FE_{NO} was not different in atopic vs nonatopic people.

There were other reasons to have anticipated an association between systemic and airway inflammation. Although CRP is thought to be a constituent of the innate immune response rather than the T_H2 or allergic response, there is a plausible mechanism for an association with asthma given that it is present in the lower respiratory tract.²⁸ C-reactive protein can be regarded as a marker for interleukin (IL) 6,²⁹ and although the role of IL-6 in asthma remains unclear, it is known to augment the level of IgE and act as a T-lymphocyte/B-lymphocyte growth factor.² Interleukin 6, along with IL-4, IL-5, IL-9, and IL-13, is produced by T_H2 cells, which are

involved in the response to allergen and the development of airway eosinophilia.¹

C-reactive protein has also been shown to influence nitric oxide synthase, although this effect seems to vary according to tissue type. For example, Ikeda et al³⁰ showed that CRP significantly decreased nitrite production (a stable metabolite of nitric oxide) in vascular smooth muscle cells. By contrast, they found that CRP enhanced inducible nitric oxide synthase expression in cardiac myocytes,³¹ whereas Verma et al³² showed that CRP decreased the production of nitric oxide by endothelial nitric oxide synthase in vascular endothelial cells. We are unaware of any studies on the direct relationship between CRP and nitric oxide production in airway tissue.

There are fewer data on fibrinogen. Plasma fibrinogen levels increase after allergen challenge,³³ but we found an overall trend to an inverse association between FE_{NO} and fibrinogen. The explanation for this is unclear. It is possible that systemic inflammation leads to increased consumption of nitric oxide in the airways. Nitric oxide is a highly reactive molecule with a relatively short half-life,³⁴ and it seems that cigarette smoking, for example, may decrease the amount of FE_{NO} through increased oxidative stress in the airways.³⁵ It is possible that there is a similar pathway with fibrinogen-mediated inflammation.

A potential weakness of this study is that we used FE_{NO} as our only indicator of airway inflammation. Although exhaled nitric oxide measurement is easy and reliable to perform and is a sensitive and specific diagnostic marker for asthma,^{11,36} it probably only reflects part of the airway inflammatory process. Fractional exhaled nitric oxide correlates with the degree of sputum eosinophilia^{9,10} but may not reflect neutrophilic inflammation. It is possible that an alternative measure of airway inflammation, such as the cellular or cytokine analysis of induced sputum, would have provided different findings. However, sputum induction would be impractical in a large population-based study. Furthermore, we also found no association between systemic inflammation and either an asthma diagnosis or skin prick test results for atopy (Table 1). Even if FE_{NO} measurement did not detect some aspect of asthmatic airway inflammation, we would expect to find an

increased level of systemic inflammatory markers with 1 of these diagnoses if a true association existed.

This study has a number of strengths. It is a population-based birth cohort with a high follow-up, providing information on asthma, smoking history, and atopy in a large sample of people who are all aged 32 years. We found no evidence of a positive association between CRP or fibrinogen and Fe_{NO} in the overall analysis. It seems unlikely that an important association between either CRP or fibrinogen and Fe_{NO} would be missed. A further analysis excluding any condition that may confound the systemic inflammation measured, such as cancer, arthritis, diabetes mellitus, and recent surgical procedures, did not alter the results (data not shown).

Our findings do not help to explain the frequently observed association between obesity and asthma.^{13,14,37} Obesity is associated with systemic inflammation, indicated by increased CRP and fibrinogen levels.^{15,16,38} In earlier analyses of this cohort up to the age of 26 years, we found that BMI was associated with asthma and airflow obstruction in women²¹ and was also associated with systemic inflammation.³⁸ An updated analysis at the age of 32 years has confirmed that BMI and adiposity are associated with asthma and airflow obstruction, but not Fe_{NO} , in women.³⁹ Our findings suggest that if there is an inflammatory link between obesity and asthma, it is not mediated by the inflammatory pathways investigated herein.

In summary, we have found no evidence that asthmatic airway inflammation, as measured by Fe_{NO} , is associated with increased levels of systemic inflammatory markers in this large population-based cohort of young adults. This lack of association persisted after adjusting for a number of potential confounding influences, including sex, smoking, and atopic status. Our conclusions are limited by the choice of airway and systemic inflammatory markers, but the findings suggest that asthma is not associated with a nonspecific systemic inflammatory response.

ACKNOWLEDGMENTS

We thank the study members and their friends and families for their continued support; Avshalom Caspi, PhD, for his comments on the manuscript; Andrew Smith, PhD, for his help in reading the nitric oxide levels; and Phil A. Silva, PhD, the study founder.

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