



Letter

Is the association between exhaled nitric oxide and asthma symptoms altered by body weight in rural adolescents?

Some studies have found that increased levels of exhaled nitric oxide (eNO) correspond to more frequent asthma symptoms.^{1,2} However, recent studies in adult and adolescent patients have suggested that obese or overweight individuals with asthma have decreased eNO levels compared with their normal weight counterparts.^{3,4} If this decreased eNO hypothesis in obesity is correct, then the association between eNO and asthma symptoms is likely to vary by body mass index (BMI; calculated as the weight in kilograms divided by square of height in meters). The purpose of this study was to determine whether the association between eNO and asthma symptoms varied by BMI in a population of teenage high school students in rural Georgia.

Patient data were collected as part of Puff City (clinicaltrials.gov Identifier: NCT01170676), a randomized clinical trial of a web-based asthma education intervention in 4 rural Georgia high schools. Baseline sociodemographic data were obtained from participating students. Because of the small percentage of other race, whites and other races were combined for analyses. A NIOX MINO⁵ device was used per manufacturer's instructions by trained research team members to obtain eNO data at baseline, end of treatment (EOT), and 6 and 12 months after treatment. This study was approved by the Augusta University Institutional Review Board and informed parental consent and child assent were obtained.

All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc), and statistical significance was assessed using an α level of .05. Descriptive statistics were determined on all variables overall and among those with 12-month EOT, BMI, and eNO data. Obesity categories were defined by age- and sex-adjusted BMI percentiles using the Centers for Disease Control and Prevention growth chart SAS program. Obesity categories included the following: normal BMI, less than 85%; overweight BMI, 85% to 94%; and obese BMI, 95% or greater. eNO was stratified into normal (≤ 25 ppb) and elevated (> 25 ppb). We used χ^2 tests to examine the association of eNO categories and obesity overall. To examine whether the association was different by race (black vs white or other race) and sex, Cochran-Mantel-Haenszel χ^2 tests were used.

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To examine whether eNO categories and obesity categories revealed differences in specific 12-month EOT asthma outcome measures, 2-factor analysis of variance (ANOVA) was used. Outcome asthma symptom variables included the number of emergency department visits in the previous 12 months, physician visits because of asthma in the previous 12 months, school days missed because of asthma in the previous 30 days, and nights awoken because of asthma in the previous 30 days. Included in each 2-factor ANOVA model were the main effects of eNO category and obesity category and the 2-factor interaction between eNO and obesity. Participants were randomly assigned to either the control or intervention group, both of which consisted of online asthma education to improve self-management of asthma symptoms. The control group received generic asthma education on websites for lung health. The intervention, referred to as Puff City, is an iterative, interactive, and culturally tailored web-based asthma education program designed for and by adolescents based on extensive feedback from a similar age population study conducted in inner-city Detroit, Michigan. The goals of the initial Detroit study were to improve asthma self-management. Each model also controlled for cohort, study arm (intervention or control), race, and sex as the outcome (BMI only) occurred after the intervention. Of statistical interest in each model is the F test for the 2-factor interaction between eNO and obesity. If the F test result for the interaction was statistically significant, the pattern of means across the obesity categories in each eNO group was different. A Tukey-Kramer multiple comparison procedure was used on the means of the interaction between eNO and obesity to examine any pairwise differences.

A total of 353 patients participated in the study. Baseline eNO revealed that 280 (79.3%) had normal values (≤ 25 ppb) and 73 (20.7%) had elevated values (> 25 ppb). Of the 353 patients, 242 had BMI and eNO data at the 12-month EOT assessment. Missing data prevented the use of 111 of the patients in the analyses. Among those in the eNO and BMI sample, approximately 60% had current asthma (defined as a physician's diagnosis and asthma symptoms in the last 12 months), the remaining students had undiagnosed asthma (multiple asthma symptoms in the previous 12 months without a physician diagnosis), 71% were black, and 40% were male (mean [SD] age, 15.5 [1.0] years). The geometric mean eNO at 12-month EOT was 24.2 ppb (95% confidence interval, 21.5–27.2 ppb), with 53% having elevated eNO levels. The mean (SD) BMI was 27.4 (7.5), and the mean (SD) BMI percentage was 81.8% (20.9%), with nearly 40% of the sample being considered obese (eTable 1).

Table 1
Two-Factor Analysis of Variance Results of eNO and Obesity on Asthma Symptoms at 12 Months^a

Outcome	Mean (SD)	F Value	P Value
School days missed because of asthma in the past 30 days			
eNO, ppb			
≤25	0.35 (2.84)	0.01	.94
>25	0.38 (2.72)		
Obesity			
Obese BMI	0.85 (4.49)	2.49	.09
Overweight BMI	0.16 (0.52)		
Normal BMI	0.02 (0.15)		
eNO × obesity			
≤25 ppb × obese BMI	0.78 (4.59)	0.31	.73
≤25 ppb × overweight BMI	0.09 (0.29)		
≤25 ppb × normal BMI	0.00		
>25 ppb × obese BMI	0.83 (4.44)		
>25 ppb × overweight BMI	0.20 (0.63)		
>25 ppb × normal BMI	0.04 (0.21)		
Nights awoken because of asthma in the past 30 days			
eNO, ppb			
≤25	0.95 (3.34)	0.66	.42
>25	1.05 (3.44)		
Obesity			
Obese BMI	1.12 (3.63)	1.78	.17
Overweight BMI	1.61 (4.72)		
Normal BMI	0.52 (1.67)		
eNO × obesity			
≤25 ppb × obese BMI	0.79 (1.87)	0.14	.87
≤25 ppb × overweight BMI	2.64 (6.79)		
≤25 ppb × normal BMI	0.29 (0.59)		
>25 ppb × obese BMI	1.43 (4.70)		
>25 ppb × overweight BMI	0.97 (2.67)		
>25 ppb × normal BMI	0.74 (2.27)		
No. of ED visits in the past 12 months			
eNO, ppb			
≤25	0.25 (0.75)	0.18	.67
>25	0.50 (1.96)		
Obesity			
Obese BMI	0.63 (2.31)	1.76	.17
Overweight BMI	0.31 (0.68)		
Normal BMI	0.17 (0.66)		
eNO × obesity			
≤25 ppb × obese BMI	0.35 (1.02)	0.88	.42
≤25 ppb × overweight BMI	0.26 (0.69)		
≤25 ppb × normal BMI	0.15 (0.42)		
>25 ppb × obese BMI	0.89 (3.04)		
>25 ppb × overweight BMI	0.34 (0.68)		
>25 ppb × normal BMI	0.20 (0.84)		
No. of physician visits because of asthma in the past 12 months			
eNO, ppb			
≤25	0.33 (0.75)	0.65	.42
>25	0.74 (2.24)		
Obesity			
Obese BMI	0.73 (2.30)	1.22	.30
Overweight BMI	0.53 (1.16)		
Normal BMI	0.38 (1.30)		
eNO × obesity			
≤25 ppb × obese BMI	0.56 (1.03)	1.29	.28
≤25 ppb × overweight BMI	0.22 (0.60)		
≤25 ppb × normal BMI	0.17 (0.38)		
>25 ppb × obese BMI	0.89 (3.04)		
>25 ppb × overweight BMI	0.74 (1.38)		
>25 ppb × normal BMI	0.59 (1.80)		

Abbreviations: ED, emergency department; eNO, exhaled nitric oxide; ppb, parts per billion.

^aA violation of the assumption of equal variance for analysis of variance (ANOVA) was detected. A nonparametric 2-factor ANOVA on the ranks of the outcome measures was performed to account for the violation. The F test statistics and corresponding P values reported are based on the analysis using the ranks. However, raw means (SDs) of the outcomes are reported within eNO, within obesity, and within eNO × obesity groups. There was no statistically significant interaction of eNO and obesity for any asthma symptom 12-month EOT outcomes, indicating that the pattern of means across obesity groups were similar among the greater than 25 ppb and 25 ppb or less eNO groups. Likewise, there were no statistically significant differences in the means of the eNO groups or weight groups.

Elevated eNO levels were not related to any of the 4 asthma symptoms studied (Table 1). Similarly, obese, overweight, and normal weight categories were not related to any of the 4 asthma symptoms. However, there is a trend of increased symptoms for obese and overweight individuals compared with normal BMI participants, but this trend is not significant. The eNO × obesity interaction term directly examines the question of whether obese, overweight, or normal body status alters the association between eNO and asthma symptoms. None of these interaction terms are significant, suggesting that BMI does not alter the association between eNO and asthma symptoms.

We also examined the association between eNO and BMI category controlling for race or sex. The association between eNO and obesity was not significant overall ($P = .39$) or after controlling for race ($P = .34$) or sex ($P = .499$) (eTable 2). There was no significant association between eNO and obesity after stratification for race (black race $P = .15$, white/other race $P = .63$) or within sex (male $P = .70$, female $P = .34$).

This is the first study, to our knowledge, to examine the association of eNO to asthma symptoms by BMI category in a southern, rural, largely black, adolescent population. Other strengths of this study are a relatively large sample generally representative of high school students in rural Georgia. The participating adolescents represented a large variation of BMIs and socioeconomic backgrounds. Limitations of the study include reliance on self-reported height, weight, and asthma symptoms. Other limitations included randomly missing data, reducing the sample size, and limited geographic diversity. Although these results did not find a direct effect of BMI on eNO, our results suggest that when clinicians use eNO for assessing asthma in patients, consideration of BMI may not be required.

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Supplementary Data

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eTable 1

Descriptive Statistics in Overall Sample and Among Those With BMI and eNO Data

Sample	Overall Sample (N = 353)	BMI/eNO Sample (n = 242)
Cohort, No. (%)		
1	200 (56.7)	153 (63.2)
2	153 (43.3)	89 (36.8)
Study arm, No. (%)		
Intervention	177 (50.1)	116 (47.9)
Control	176 (49.9)	126 (52.1)
Asthma type, No. (%)		
Current asthma	210 (59.5)	143 (59.1)
Symptoms only	143 (40.5)	99 (40.9)
Race, No. (%)		
Black	238 (68.0)	170 (70.5)
White/other	112 (32.0)	71 (29.5)
Sex, No. (%)		
Male	132 (37.4)	96 (39.7)
Female	221 (62.6)	146 (60.3)
Age, mean (95% CI)	15.5 (15.4–15.6)	15.4 (15.2–15.5)
eNO at 12 months, ppb, mean (95% CI)		24.2 (21.5–27.2)
eNO categories at 12 months, ppb		
≤25		114 (47.1)
>25		128 (52.9)
BMI, mean (95% CI)		27.4 (26.4–28.3)
BMI percentage, mean (95% CI)		81.8 (79.1–84.4)
Obesity, No. (%)		
Obese BMI		90 (37.2)
Overweight BMI		58 (24)
Normal BMI		94 (38.8)
Days of school missed because of asthma in the past 30 days, mean (95% CI)		0.4 (0.0–0.7)
Nights awoken because of asthma in the past 30 days, mean (95% CI)		1.0 (0.6, 1.4)
ED visits in the past 12 months, mean (95% CI)		0.4 (0.2, 0.6)
Physician visits because of asthma in the past 12 months, mean (95% CI)		0.5 (0.3, 0.8)

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by square of height in meters); CI, confidence interval; ED, emergency department; eNO, exhaled nitric oxide; ppb, parts per billion.

eTable 2The χ^2 Test for the Association Between eNO and Obesity Overall and the CMH Test Controlling for Race and Sex

eNO, ppb	Obesity, No. (%)			χ^2 Value	P Value	CMH P Value
	Obese BMI	Overweight BMI	Normal BMI			
Overall						
≤25	43 (47.8)	23 (39.7)	48 (51.1)	1.90	.39	
>25	47 (52.2)	35 (50.3)	46 (48.9)			
Black race						.34
≤25	36 (56.3)	17 (39.5)	36 (57.1)	3.80	.15	
>25	28 (43.7)	26 (60.5)	27 (42.9)			
White/other race						
≤25	7 (26.9)	6 (40.0)	11 (36.7)	0.91	.63	
>25	19 (73.1)	9 (60.0)	19 (63.3)			
Male						.499
≤25	18 (60.0)	13 (61.9)	31 (68.9)	0.71	.70	
>25	12 (40.0)	8 (38.1)	14 (31.1)			
Female						
≤25	25 (41.7)	10 (27.0)	17 (34.7)	2.17	.34	
>25	35 (58.3)	27 (73.0)	32 (65.3)			

Abbreviations: BMI, body mass index; CMH, Cochran-Mantel-Haenszel; eNO, exhaled nitric oxide; ppb, parts per billion.