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Is the relationship between eNO and asthma symptoms altered by body weight in rural adolescents?

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eNO; obesity; rural; asthma; adolescents

Some studies have shown 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 asthmatic individuals have decreased eNO levels compared to their normal weight counterparts.^{3,4} If this decreased eNO hypothesis in obesity is correct, then the relationship between eNO and asthma symptoms is likely to vary by Body Mass Index (BMI). The purpose of this study was to determine whether the relationship 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”, a randomized controlled trial (RCT) of a web-based asthma education intervention in four rural Georgia high schools. Baseline sociodemographic data were obtained on participating students. Due to 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 then at 6 and 12 months after treatment. This study was approved by the Augusta University IRB and informed parental consent and child assent were obtained.

All statistical analyses were performed using SAS 9.4 and statistical significance was assessed using an alpha level of 0.05. Descriptive statistics were determined on all variables overall and among those with 12 months EOT, BMI, and eNO data. Obesity categories were

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defined by age and sex-adjusted BMI percentiles using the CDC growth chart SAS program. Obesity categories included: normal-BMI < 85%, overweight BMI 85–94%, and obese BMI ≥ 95%. eNO was stratified into normal ≤ 25ppb and elevated >25ppb. Chi-square tests were used to examine the relationship of eNO categories and obesity overall. To examine whether the association was different by race (black versus white/other race) and gender, Cochran-Mantel-Haenszel chi-square tests were used.

To examine whether eNO categories and obesity categories combined showed differences in specific 12-month EOT asthma outcome measures, two-factor ANOVA was used. Outcome asthma symptomatology variables included the number of: ER visits in the previous 12 months, doctor visits due to asthma in the previous 12 months, school days missed due to asthma in the previous 30 days, and nights awoken due to asthma in the previous 30 days. Included in each two-factor ANOVA model were the main effects of eNO category and obesity category and the two-factor interaction between eNO and obesity. Participants were randomly assigned to either the control or intervention group, both of which consisted of on-line 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. 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 gender as the outcome (BMI only) occurred following the intervention. Of statistical interest in each model is the F-test for the two-factor interaction between eNO and obesity. If this F-test 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 pair-wise differences.

There were 353 subjects who participated in the study. Baseline eNo revealed 79.3% (N=280) had normal values (≤ 25ppb) and 20.7% (N=73) had elevated values (>25ppb). Of the 353 subjects, 242 had BMI and eNO data at 12 month EOT assessment. Missing data prevented the use of 111 of the subjects in the analyses. Among those in the eNO and BMI sample, approximately 60% had current asthma (defined as a doctor’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 age 15.5 (SD=1.0) years. The geometric mean eNO at 12 months EOT was 24.2 (95% CI: 21.5–27.2) ppb with 53% having elevated eNO levels. The mean BMI was 27.4 (SD=7.5) and the mean BMI% was 81.8 (SD=20.9) with nearly 40% of the sample being considered obese as shown in Supplemental Table 1.

Elevated eNO levels were not related to any of the four asthma symptoms studied as seen in Table 1. Similarly, obese, overweight, and normal weight categories were not related to any of the four asthma symptoms. However, there is a trend of increased symptoms for obese and overweight individuals compared to normal BMI participants, but this trend is not significant. The “eNO x Obesity” interaction term directly examines the question whether obese, overweight or normal body status alters the relationship between eNO and asthma

symptoms. None of these interaction terms are significant suggesting that BMI does not alter the relationship between eNO and asthma symptoms.

We also examined the association between eNO and BMI category controlling for race or gender. The association between eNO and obesity was not significant overall ($p=0.3868$) or after controlling for race ($p=0.3375$) or gender ($p=0.4987$) as shown in Supplemental Table 2. There was no significant association between eNO and obesity after stratification for race (black race $p=0.1495$, white/other race $p=0.6321$) or within gender (male $p=0.7025$, female $p=0.3385$).

This is the first study to examine the relationship 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 body mass indexes and socioeconomic backgrounds. Limitations of the study include reliance on self-reported height, weight and asthma symptoms. Other limitations included: randomly missing data reducing sample size and limited geographic diversity. While these results did not find a direct effect of BMI on eNO, our results suggest that as clinicians use eNO for assessing asthma in patients, consideration of BMI may not be required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations/Acronyms

eNO	exhaled Nitric Oxide
BMI	Body Mass Index
EOT	End of Treatment

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Table 1
Two-Factor ANOVA Results of eNO and Obesity on Asthma Symptomatology at 12 months *

Outcome	Effect	Level	Mean	SD	F-value*	p-value*
School Days Missed due to Asthma in Past 30 days	eNO	25	0.35	2.84	0.01	0.9361
		> 25	0.38	2.72		
	Obesity	Obese	0.85	4.49	2.49	0.0853
		Overweight	0.16	0.52		
		Normal	0.02	0.15		
	eNO x Obesity	25 – Obese	0.78	4.59	0.31	0.7320
		25 – Overweight	0.09	0.29		
		25 – Normal	0.00	0.00		
		> 25 – Obese	0.83	4.44		
		> 25 – Overweight	0.20	0.63		
Nights Awoken due to Asthma in Past 30 days	eNO	> 25 – Normal	0.04	0.21	0.66	0.4169
		25	0.95	3.34		
	Obesity	> 25	1.05	3.44	1.78	0.1703
		Obese	1.12	3.63		
		Overweight	1.61	4.72		
	eNO x Obesity	Normal	0.52	1.67	0.14	0.8665
		25 – Obese	0.79	1.87		
		25 – Overweight	2.64	6.79		
		25 – Normal	0.29	0.59		
		> 25 – Obese	1.43	4.70		
Number of ED Visits in Last 12 Months	eNO	> 25 – Overweight	0.97	2.67	0.18	0.6721
		> 25 – Normal	0.74	2.27		
		25	0.25	0.75		
	Obesity	> 25	0.50	1.96	1.76	0.1740
		Obese	0.63	2.31		
		Overweight	0.31	0.68		

Outcome	Effect	Level	Mean	SD	F-value*	p-value*
	eNO x Obesity	Normal	0.17	0.66		
		25 – Obese	0.35	1.02	0.88	0.4152
		25 – Overweight	0.26	0.69		
		25 – Normal	0.15	0.42		
		> 25 – Obese	0.89	3.04		
		> 25 – Overweight	0.34	0.68		
		> 25 – Normal	0.20	0.84		
	eNO	25	0.33	0.75	0.65	0.4217
		> 25	0.74	2.24		
		Obese	0.73	2.30	1.22	0.2985
	Obesity	Overweight	0.53	1.16		
		Normal	0.38	1.30		
		25 – Obese	0.56	1.03	1.29	0.2766
		25 – Overweight	0.22	0.60		
		25 – Normal	0.17	0.38		
		> 25 – Obese	0.89	3.04		
		> 25 – Overweight	0.74	1.38		
		> 25 – Normal	0.59	1.80		

* It should be noted that a violation of the assumption of equal variance for ANOVA was detected. A non-parametric two-factor ANOVA on the ranks of the outcome measures was performed to account for the violation. The F-test statistic and corresponding p-value reported are based on the analysis using the ranks. However, raw means and standard deviations of the outcomes are reported within eNO, within obesity and within eNO and obesity groups. There was no statistically significant interaction of eNO and obesity for any asthma symptomatology 12-months EOT outcomes indicating that the pattern of means across obesity groups were similar among the >25 and 25 eNO groups. Likewise there were no statistically significant differences in the means between eNO groups or between obesity groups.